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## ORIGINAL ARTICLE

# Comparison of Diagnostic Yield in Single Vs Multiple Needle Passes in Endoscopic Ultrasound Guided Fine Needle aspiration cytology in Abdominal Solid Lesions and Abdominal lymphnodes at Tertiary Care Centre

**Shivani Meena*, Dilip Ramrakhiani**, Rimjhim Shrimal***, Sandeep Nijhawan****, Ashok Jhajharia*****, Deepti Yadav***


## ABSTRACT

**Introduction:** Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) is the accurate diagnostic method for abdominal solid masses, mediastinal masses and lymph nodes. Endoscopic ultrasound has proven to be a highly sensitive tool for diagnostic lesions in and adjacent to the gastrointestinal tract. EUS-FNA is not a difficult technique but it requires adequate experience.The present study was done to compare the diagnostic yield of single needle pass vs multiple needle passes.

**Methods**: It was an observational hospital based study. There were two groups made with 30 samples each. Duration of study was 6 months. Consecutive sample were taken with inclusion criteria of age more than 15 years and solid masses. Fine needle aspiration by done using endoscopic ultrasound in department of gastroenterology.

**Results:** Two groups were made which were single needle and multiple needle passes. Mean number of passes in pancreatic masses and lymph node were 3.1 and 2 respectively. Cellularity was significantly different in the two groups having higher cellularity in group II. There was no significant difference in the definitive diagnosis between the two groups.

**Conclusion:** Higher cellularity observed in group of patients with multiple needle passes was statistically significant but the higher diagnostic yield observed in this group was not statistically significant due to limited sample size.


**Keywords:** Endoscopic Ultrasound, FNAC, Needle passes, Diagnostic Yield

## INTRODUCTION

Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) is the accurate diagnostic method for abdominal solid masses and mediastinal masses and lymph node and its accuracy is affected by various FNA methods and EUS equipment.

Endoscopic ultrasound (EUS)-guided fine needle aspiration (FNA) has been used for diagnosis of pancreatic solid masses. EUS-FNA has a reported sensitivity of 54% to 95%, a specificity of 71% to 100%, and an accuracy of 85% to 90%. The foundation for the diagnostic accuracy of EUS-FNA is obtaining adequate tissue, and it could be influenced by several variables, including the size of the lesion, location of the lesion, needle gauge, needle type, use of a stylet and suction, number of needle passes, the endosonographer's skill and experience, and on-site cytopathology evaluation.

Endoscopic ultrasound has proven to be a highly sensitive tool for diagnostic lesions in and adjacent to the gastrointestinal tract. EUS-FNA is not a difficult technique but it requires adequate experience. Interestingly, some of the easiest cases provide information that can have a tremendous impact on patient management[1,2].

The goal of performing FNA is to obtain a positive diagnosis in the quickest possible time with least number of passes. The number of passes to be made depends on the presence or absence of on-site cytopathologist for assessment of specimen adequacy, establishment of onsite diagnosis and to guide the need for further sampling. In the absence of an on-site pathologist,

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adequate passes should be performed to avoid the need for repeat procedure[3].

EUS-FNAC help us to get diagnostic material which give us information to guide disease specific therapeutic intervention. This techniques causes prevention of unnecessary operative procedure. The usefulness of EUS-FNA depends on several factors. In addition to the experience of the endoscopist, adequate sampling, adequate sample processing, better communication between the cytopathologist and the endoscopist, accurate interpretation by the cytopathologist, and the ability to determine the need for additional samples required for ancillary studies are needed for effective diagnosis[4].

Several studies in the last year focused on the technical aspects of EUS-FNA like optimal needle choices, variety of sampling method and different techniques of specimen[5,6]. Although there is wide use of EUS-FNA, there still exists a wide variation in the number of samples required to ensure acquisition of diagnostic material from different kind of lesions[7].

In the presence of an onsite pathologist, the smears are quickly processed and examined by light microscopy in the endoscopic suit and immediate feedback is given to endosonographer. This information can be used in guiding the number of EUS-FNA passes required to obtain a final diagnosis. It evaluates whether the aspirate is diagnostic or non-diagnostic[8]. When on-site cytological evaluation is unavailable, ESGE suggests performing of three to four needle passes with an FNA needle or two to three passes with a fine needle biopsy needle[9].

The present study was conceived to assess and compare the diagnostic yield of sample obtained from EUS-FNA from abdominal solid lesions and lymphnode in a single needle pass v/s multiple needle passes.

## MATERIALS AND METHOD

**Study Design**: Descriptive observational study.

**Sample Size:** Sample size was calculated with 95% confidence level and alpha error of 0.05 assuming 57.7% and 85.7% diagnosis was achieved in patients on pass one by standard and fanning technique respectively as given by Bang et al[10]. At a study power of 80% the required sample size was 30 patients for each group.

**Study Duration**: Duration of study was July 2019 to Jan 2020.

**Study Universe:** EUS Guided FNA done in one needle pass and multiple needles pass in Gastroenterology Department of Medical College and attached hospitals, Jaipur.

**Inclusion Criteria:** The inclusion criteria were as follows:

1. Age $\geq$15 years,
2. Abdominal solid masses including lymph nodes identified by the investigational modalities.

**Exclusion Criteria**: The exclusion criteria were as follows:

1. Coagulopathy (international normalized ratio of >1.5 or platelet count of <50,000/mm3)
2. Presence of intervening blood vessels, and altered gastrointestinal anatomy.
3. Cystic Masses.

**Sampling Technique**: Every consecutive eligible EUS guided FNA done in Gastroenterology Department at SMS Hospital, Jaipur.

**Study Tool**: Fine Needle Aspiration (FNA) done by endoscopic ultrasound in Gastroenterology Department in the patient who had G.I. solid lesions and/or lymph nodes.

### EUS-FNA Procedures

EUS-FNA procedures were performed using a standardized method in patients who were under conscious sedation with intravenous midazolam and propofol. All procedures were carried out using a linear array echo endoscope (GF UCT180; Olympus Medical Systems, Tokyo, Japan) in conjunction with EVIS EXTRA CLV-180 light source.

The needle size was chosen to fit the situation randomly by endosonographer. A standard 19-, 22-, or 25-G FNA device (Echo Tip; Cook Medical, Bloomington, IN) was employed for EUS-FNA. The capillary (slow pull) technique was employed for EUS-FNA mostly. In some cases, we applied suction technique during EUS-FNA in order to increase the quantity of the FNA sample. Pancreatic head masses were approached from the duodenum, whereas pancreatic body and tail masses were

accessed from the stomach. The adequacy of obtained specimens was judged by the presence of macroscopic material without cytopathologist, and the puncture was repeated until adequate specimens are obtained. After the masses were punctured by the needle, the stylet was withdrawn and the needle moved backward and forward within the masses 10 to 15 times per pass. The needle was then removed. The aspirated specimen was expressed onto slides by reinsertion of the stylet within the needle and air flushing, if needed.

**Statistical Analysis:** Sample size was selected on the basis of sample size calculation formula for difference of effect size proportions in the two groups. The statistical tests used in the study are unpaired Student's *t*-test for continuous variables and Chi-square test for categorical variables. Mann-Whitney test was used to assess the diagnostic yield by different number of needle passes in EUS-FNA. SPSS version 20.0 was used for statistical analysis. Data were expressed as mean ± standard deviation. Value of $P < 0.05$ is considered significant.

## RESULTS

Patient in group I were slightly younger than group II with mean age of 47.4 years in group I as compared to group II (49.6years)(Table 1). In the both groups males were predominant with overall affected male to female ratio of 3:1.Including both groups (single pass and multiple passes) pancreas was the most common site (28.5%) followed by abdominal lymph nodes (26.6%). (Table 2)

**Table 1: Baseline characteristics of EUS-FNA according to number of the needle passes used in abdominal organs and lymph nodes**

| Variables | Single needle pass (Group I) | Multiple needle passes (Group II) |
|---|---|---|
| Age in years (range) | 47.4±15.36 (15-75) | 49.6±15.36 (30-70) |
| Sex (Males:Females) | 22:8 | 23:7 |
| Size of Tumour | 24.7±13.3 (10-70) | 29.97±19.37 (10-80) |
| Cellularity | 18/30 | 26/30 |
| Definitive Diagnosis | 25/30 | 27/30 |

**Table 2: Distribution of patients according to target regions**

| EUS-FNA Site | No. of Cases (60) | % of Cases (Out of 100) |
|---|---|---|
| Pancreas | 17 | 28.5% |
| Abdominal Lymph Node | 16 | 26.6% |
| Mediastinal Lymph Node | 9 | 15% |
| Liver | 8 | 13.5% |
| Common Bile Duct | 4 | 6.6% |
| Spleen | 3 | 5% |
| Duodenum | 1 | 1.6% |
| Gastric Mass | 1 | 1.6% |
| Gall Bladder | 1 | 1.6% |

In second group of multiple passes more no. of passes were three (43.3%) followed by two passes (26.6%) and 4 passes (16.6%) (Figure 1). Mean number of needle passes used in pancreas were 3.1 needle passes for diagnosis. While in 25 cases of lymph nodes mean number of needle passes were 2.

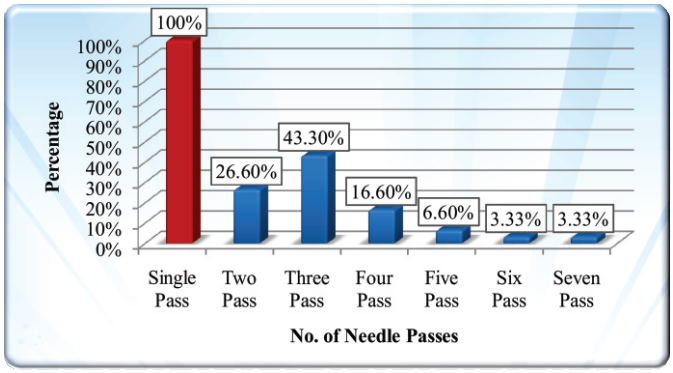


**Figure 1: Distribution of patients according to no. of needle passes**

In 30 cases where single needle was passed using EUS guided FNA, there was cellularity in 22 cases (73.3%) and 8 cases were non cellular (26.6%). In EUS-FNA using multiple passes (⩾ 2 passes), the frequent number of passes used were 3 in which cellularity was found in 8 cases and 1 case was non cellular. Cellularity was 26/30 in Group II and it was significantly different from Group I (p=0.0013).

**Table 3: Distribution of patients according to number of pass and Cellularity (Group II)**

| No. of the Needle Passes | Cellularity No. of Cases) | Non-Cellular (No. of Cases) |
|---|---|---|
| 2 Passes | 7 | 2 |
| 3 Passes | 8 | 1 |
| 4 Passes | 6 | 1 |
| 5 Passes | 2 | 0 |
| 6 Passes | 1 | 0 |
| 7 Passes | 1 | 0 |

The final cytopathological diagnosis was reported (malignant or benign cases) in14 cases (46.6%) out of 30 cases in Group I as compared with 15 cases out of 30 cases (50%) in group II. Other categories included were inconclusive diagnosis and non-diagnostic cases (Table 4).

**Table 4: Distribution of cases according to number of needle passes and cytopathological diagnosis**

| | Diagnosis | Group I (Single Pass) | Group II (Multiple Pass) |
|---|---|---|---|
| Malignant cases | Pancreatic Carcinoma | 4 (13.3%) | 4 (13.3%) |
| | Lymphoma | 3 (10%) | 1 (3.4%) |
| | Hepatocellular Carcinoma | 2 (6.6%) | 4 (13.3%) |
| | Metastatic lymph node | 4 (13.3%) | 4 (13.3%) |
| Benign cases | GIST | 1 (3.4%) | 0 |
| | Granulomatous lesion | 1 (3.4%) | 0 |
| | Psuedocyst of pancreas | 0 | 1 (3.4%) |
| | Tubercular lymphadenopathy | 4 (13.3%) | 3 (10.1%) |
| | Reactive hyperplasia | 4 (13.3%) | 4 (13.3%) |
| | Inconclusive Diagnosis | 2 (6.7%) | 5 (16.6%) |
| | Non Diagnostic Cases | 5 (16.6%) | 4 (13.3%) |

On statistical analysis, there was no significant difference in the definitive diagnosis between single pass and multiple pass needle (Table 5).

**Table 5: Association between number of passes and cellularity**

| | Single pass n (%) | Multiple pass n(%) | Total | p-value |
|---|---|---|---|---|
| Cellularity present | 18 (40.9) | 26 (59.1) | 44 (100) | 0.013 |
| Non-cellular | 12 (75) | 4 (25) | 16(100) | |
| Total | 30(50) | 30(50) | 60 (100) | |

*Fisher exact test

## PHOTOGRAPHS

### Group I (Single needle pass EUS FNA)

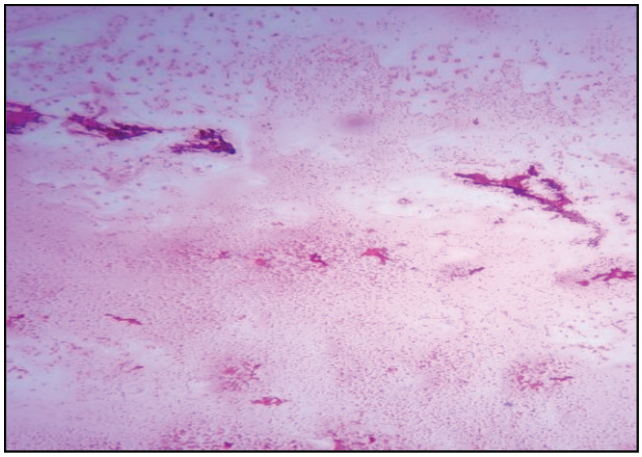

**Figure 2: EUS FNA from Gall Bladder Mass- hypocellular smear showing few cells enmeshed in blood clot. (H&E, 40X)**

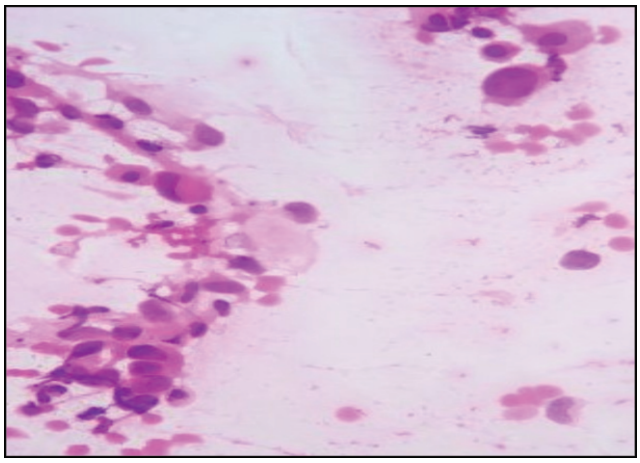

**Figure 3: High power view showing few benign cells only. Inadequate for diagnosis (H&E, 400x)**

### GROUP II (MULTIPLE NEEDLE PASSES EUS-FNA)

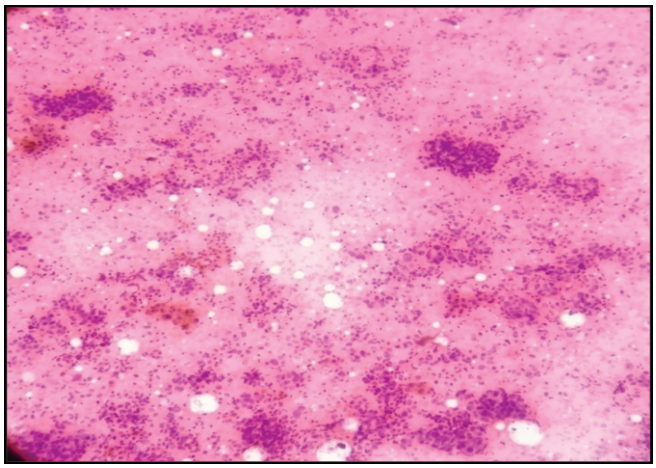

**Figure 4: EUS FNA from head of pancreas- abundant cellularity (H&E, 40X)**

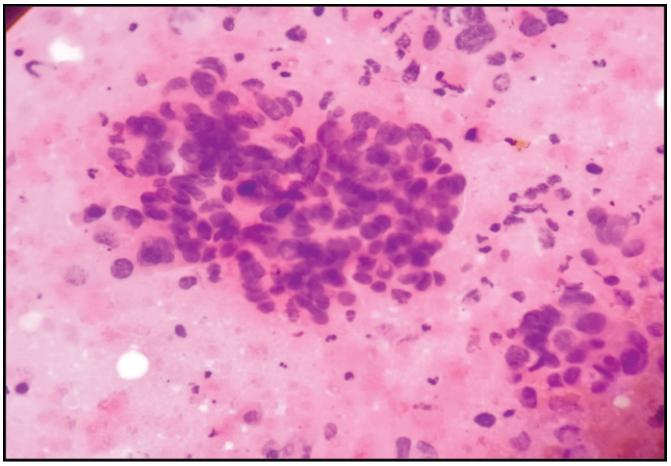

**Figure 5: High power view showing cells in adenomatous pattern with pleomorphism and high N:C ratio- Moderately differentiated adenocarcinoma of pancreas (H&E 400X)**

## DISCUSSION

In present study there were two groups including single needle pass and multiple needle passes in EUS – FNA cases. The number of needle passes and diagnostic yield were not significantly affected with the age of the patients. As Iglesias et al. conducted a studied 182 cases and found no association with age, sex, location and size of lesions[11]. In the present study, more common target sites for EUS-FNA were pancreas (17 out of 60 cases) and lymph nodes (16 out of 60 cases). Similarly, Bang et al conducted a prospective study of 95 consecutive patients who underwent EUS FNA, for diagnosis or staging, of 95 sites: pancreas (33), Lymph node (43), and miscellaneous (19)[10].

In group II (multiple number of needle passes) frequently used number of needle passes were three (13 out of 30 cases) with mean number of needle passes in current study as 3.26. Itoi et al found that even without ROSE, mean 2.88 needle passes were adequate for diagnosis with 93.3% accuracy[12]. When ROSE is not available there is more number of needle passes needed. Which is in concordance in our findings in multiple needle passes. There were 30 cases of single needle passes, diagnosis was possible in 22 cases out of 33 (cellularity 73.3%). Lim et al described that single pass can also be used for definitive diagnosis which varies according to target sites[13].

There was more cellularity in cases of group II. 26 cases out of 30 cases (86%) were cellular for diagnosis and p-value for this association was 0.013 which is significant. Cellularities were affected by number of needle passes. For pancreas and lymph nodes the mean number of passes required were 3.1 and 2 respectively. In our study greater cellularity yield was observed in multiple needle passes as compared to single pass (statistically significant, p-value=0.013). This is in concordance with the various studies. Erickson et al. showed that 5 to 6 passes were required for pancreatic masses, meant that multiple passes were needed to obtain accurate diagnosis[14]. Also, Le Blanc et al. illustrated in a study that increase in sensitivity from 17% to 87% when more than 7 passes were made with a 22 G needle into pancreatic masses[15].

Turner et al. demonstrated in their study that 3 to 4 passes were necessary to achieve a diagnostic accuracy of 80%[16]. Suzuki et al. described in a study involving 25 G needle, 4 passes were found to be sufficient for EUS FNA of solid pancreatic lesions[17]. Bluen et al. stated in an article that several factors can be responsible for diminished accuracy of abdominal and mediastinal area. More number of needle passes need to make out diagnosis[18].

Per-pass analyses of data from some studies in patients with pancreatic masses showed that three to four passes with an FNA needle to achieve high rates of diagnostic samples and high sensitivity for malignancy, which is more than 90%[19-24]. A lower number of passes was associated with suboptimal performance. On the other hand, increasing the number of needle passes more than four (FNA) or three marginally improved the results[20,23,24]. However, also for the smaller tumors, increasing the number of passes beyond four only marginally improved the sensitivity. Per-pass analysis in patients with lymphadenopathy found that sensitivity for malignancy reaches 100% after three passes with an FNA needle[24]. Binmoeller attributed that cellularity and adequacy differ when there is on site cytopathologist was not available[25]. Even ESGE criteria recommend multiple passes for various organs as was observed in our study[26].

The diagnostic yield in the multiple pass group was 51% and this was higher than the diagnostic yield in single needle pass group (49%). Although this result is not statistically significant due to limited sample size (limitation of study) but this has also been shown in several studies mentioned previously involving larger number of patients that multiple needle passes associated with high diagnostic adequacy.

## CONCLUSION

In this study, greater cellularity and diagnostic yield were observed in group of patients subjected to multiple needle passes. The higher cellularity observed in group of patients with multiple needle passes was statistically significant but the higher diagnostic yield observed in this group was not statistically significant due to limited sample size.

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## ORIGINAL ARTICLE

# Comparative Randomized Study of Balanced Salt Solution and Ringer Lactate Fluid Administration on Plasma Electrolytes, Acid Base Status and Renal Function in Cardiac Surgeries

**Anjum Saiyed*, Yogendra Singh**, Reema Meena***


## ABSTRACT

**Background:** Intraoperative fluid therapy is an integral part of anaesthesia management[1]. Proper fluid therapy intra operatively will avoid hypovolemia and hypotension also maintains proper tissue perfusion and oxygen Patient who have to undergo cardiac surgery present a major challenge to the anaesthetist. No solution is ideal for fluid therapy in cardiac surgery.

This study was carried out with the aim to compare and assess Balance salt solution and Ringer Lactate (RL) fluid administrations on plasma electrolytes, acid base status and renal function in patient undergoing cardiac surgeries on cardiopulmonary bypass.

**Method:** All patients were managed by standard institutional protocol and were randomly distributed in two groups according to fluid administered intravenously and priming solution used in cardiopulmonary bypass circuit. Total Cases [Group A (n=40) + Group B (n=40) = 80]

**Group A (n=40):** received balanced salt solution intravenous (5ml/ kg /hour) and in the priming solution 1500 ml + 6% hydroxy ethyl starch 500ml (130/0.42)

**Group B (n=40):** received RL intravenous (5ml/ kg /hour) and in the priming solution1500 ml + 6% hydroxy ethyl starch 500ml (130/0.42). Primary variables recorded are plasma electrolytes (sodium, chloride), lactate, bicarbonate, pH levels. Secondary variables blood glucose, serum creatinine levels, hemodynamic parameters (HR, MAP, CVP, Spo2) were noted at the interval mentioned Base line (T0), after anaesthesia induction (T1), before going on bypass (T2 ), after coming of bypass (T3), at the end of surgery (T4) : 2 hr after surgery (T5) and 24 Hr after beginning of surgery (T6). Continuous data were summarized in from of mean and standard deviation. The difference in means was analyzed using student t- test. Count data were summarized in form of proportions. The difference in proportions was analyzed using Chi-Square test. The level of significance was kept 95% for all statistical analysis

**Results:** There were no statistically significant differences in the demographic data between the two groups. In both the groups all variables were comparable at baseline. There is hyperchloremia in group B than group A at interval T5 and T6. The mean $HCO_3^-$ was significantly higher in group A than group B at interval T3,T5,T6. The mean Lactate lavels were significantly higher in group B than group A at all the time intervals. The difference in mean blood glucose lavels was found to be statistically significantly high at T2, T4, T5, T6 time intervals.

No complications with balanced salt solution and ringer lactate were encountered.

**Conclusion:** The balanced salt solution is better fluid than ringer lactate solution due to reduced incidence of hypercloramic metabolic acidosis and less increased level of serum glucose and lactate. Renal functions are better preserved in Balance salt solution.


**Key Words:** Balanced salt solution, Ringer lactate, Cardiopulmonary bypass.


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## INTRODUCTION

Intra operative fluid therapy is an integral part of anaesthesia management[1]. Proper fluid therapy during surgery will avoid hypovolumia, hypotension and maintains proper tissue perfusion and oxygenation. Hypotension can be avoided by proper diagnosis and treatment of the underlying cause. Important causes of hypotension are blood loss, fluid depletion, third space losses, evaporative losses from wound, hypoxia and vasodilatory effect of anaesthetic agent. Fluid therapy should not only lead to stabilization of macro circulation, but also of microcirculation. Microcirculation especially seems to be affected by different volume substitution fluid. Physiology and pathophysiology of fluid compartment should be accounted for when decision has to be made among different solution[2]. Patient who have to undergo cardiac surgery present a major challenge to the anaesthetist beyond the problem of fluid therapy. In cardiac patient oedema is due to water and salt retention so total body water and sodium is more in these patient but retention of water is more than that of salt so hyponatremia is frequently seen which is dilutional. Remember that hyponatremia is usually dilutional and need fluid restriction. In cardiac patient when diuretics instituted urine output will increase and will not follow routine guidelines of fluid replacement. So our aim is to remove extra fluid from the body by restricting fluid intake despite good urine output. During cardiac surgery the patients may experience extreme condition like cardiac arrest or deep hypothermia unlike any other sub speciality. In the immediate postoperative period, relative insufficiency of blood volume often occurs, especially use of cardiopulmonary bypass often induces capillary leakage which may lead to interstitial oedema during concomitant intravasal volume depletion[3]. Maximising the cardiac output by fluid infusion benefits patient undergoing cardiac surgery but they may not tolerate large volume of fluid due to impaired cardiac performance hence fluid resuscitation without or with minimal risk of fluid excess might be beneficial. A perfect balanced fluid could be considered to be one in which any change induces in total concentration of non volatile weak acid is offsets by a change in strong ion difference so that pH remain stable[4]. No fluid is perfect fluid for perioperative volume replacement in the extracellular space during cardiac surgery.

Currently available balanced crystalloid solution have lower overall osmolarity than 0.9 % NaCl with a lower Sodium (Na) concentration and much lower lower chloride ion (Cl) concentration. Reduction in anionic content is compensated for by the addition of stable organic anion buffer such as lactate, gluconate or acetate. Colloid intravascular fluid therapy affects acid base balance and can cause iatrogenic acidosis. Which is the result of administration chloride rich fluid and administration of sodium bicarbonate to correct acidosis.

This study was carried out with the aim to compare and assess Balance salt solution (BBS) and Ringer Lactate (RL) fluid administrations on plasma electrolytes, acid base status and renal functions in patient undergoing cardiac surgeries on cardiopulmonary bypass (CPB).

## MATERIALS AND METHODOLOGY

It is a Hospital based, prospective randomized double blind, Interventional study. Total 80 Cases, 40 in each group were studied. Randomization was done by sealed envelope method & blinding was done by covering the solution bottle with paper bag.

**Group A (n=40)** received balanced salt solution (BSS) intravenous (5ml/ kg /hour) and in the priming solution1500 ml + 6% hydroxyethyl starch 500ml (130/0.42)

**Group B (n=40)** received RL intravenous (5ml/ kg /hour) and in the priming solution1500 ml + 6% hydroxyethyl starch 500ml (130/0.42).

Patients of either sex undergoing cardiac surgery, ASA Grade II, III, age 30-60 Years, weighting 40-60 kg with normal coagulation profile liver and kidney functions were included. Thorough pre anaesthetics check up and written informed consent was obtained.

Patients with congestive heart failure, renal, liver and respiratory disorder, emergency and redo surgery were excluded from the study.

After confirming written informed consent and fasting status, patients were taken in the operation theatre. 18G intravenous cannula was secured and study fluid was started @ 5ml/kg/hr in peripheral line according to the assigned group. 12 lead ECG and pulse oximeter were attached. Patients were premedicated with injection morphine 0.1 mg/kg intramuscular (IM) and injection promethazine 0.5 mg/kg (IM). Femoral artery cannulation was performed and central venous catheter

was inserted into right internal juglar vein under local anaesthesia. Base line parameter were recorded in the form of Heart Rate (HR), Systolic blood pressure (SBP), Diastolic Blood Pressure (DBP), Mean Arterial Pressure (MAP), Central venous pressure (CVP) and Arterial Blood Gas(ABG). Patients were preoxygenated with 100% Oxygen for 3 min. Induction of anaesthesia was done with inj midazolam 0.05 mg/kg, inj. fentanyl 5µg/kg & Inj. Etomidate 0.3mg/kg IV slowly over a period of 60-90 second until there was loss of eyelash reflex. Inj. Rocuronium bromide 0.9 mg/kg I.V. was given to facilitate the intubation. Oral tracheal intubation was attempted by appropriate sized cuffed endotracheal tube at 2 min after induction. Position of tube was checked and secured with adhesive. HR, MAP, CVP were recorded. Anaesthesia was with 100% O2, inj. midazolam 0.01mg/kg hourly, inj. Vecuronium 0.05 mg/kg every half hourly. Nasopharyngeal temperature probe and nasogastric tube were secured. Patients were catheterised with Foleys urinary catheter and urine output was measured. Patient taken on cardio pulmonary bypass circuit which was primed with 1500 ml balanced salt solution+ 500ml 6% Hydroxy ethyl in Group-A, 1500ml RL + 500ml 6% Hydroxy ethyl starch (130/0.42) in group B.

After completion of surgery patients were shifted to ICU. Extubation criteria include adequate level of consciousness, muscle strength, stable cardiovascular status, normothermia, adequate pulmonary function and minimal thoracotomy tube drain.

Primary variables plasma electrolytes Sodium, chloride, lactate, bicarbonate and pH level. Secondary variables blood glucose, serum creatinine levels, hemodynamic parameters (HR,MAP) were noted at the interval mentioned Base line(T0), After anaesthesia induction(T1), Before going on bypass (T2 ), After coming off bypass(T3), At the end of surgery (T4), 2 hour after surgery (T5) and 24 Hours after beginning of surgery(T6).

Data were summarized in from of mean and standard deviation. The difference in means was analyzed using student t- test. Count data we form of proportions. The difference in proportions was analyzed using Chi-Square test. The level of significance was kept 95% for all statistical analysis re summarized in form of proportions. The difference in proportions was analyzed using Chi-Square test. The level of significance was kept 95% for all statistical analysis.

## RESULTS

There were no statistically significant difference in the demographic data between the two groups .In both the groups all variables were comparable at baseline. (Table 1, 2).

**Table 1: Showing Demographic data and other variables**

| | Group A | | Group B | | P Value | Significance |
|---|---|---|---|---|---|---|
| Mean Age (years) | Mean | SD | Mean | SD | | |
| | 39.80 | 8.13 | 39.65 | 8.09 | 0.934 | N.S. |
| Mean Weight (kg) | 48.80 | 7.29 | 49.26 | 7.33 | 0.783 | N.S. |
| Mean Height (cm) | 147.70 | 8.04 | 148.35 | 8.27 | 0.722 | N.S. |
| Duration of Surgery (Hours) | 2.70 | 0.56 | 2.48 | 0.51 | 0.064 | N.S. |

**Table 2: Showing Demographic data and other variables**

| | Group A | | Group B | |
|---|---|---|---|---|
| | No. | % | No. | % |
| ASA Grade 2 | 25 | 62.5 | 23 | 57.5 |
| ASA Grade 3 | 15 | 37.5 | 17 | 42.5 |
| Total | 40 | 100.00 | 40 | 100.00 |
| | No. | % | No. | % |
| Male | 19 | 47.5 | 15 | 37.5 |
| Female | 21 | 52.5 | 25 | 62.52 |

Baseline variables were comparable in both the groups at different time intervals.

It was observed that there was no significant difference in mean heart rate, among both the groups at different time intervals.

There was no statistical significant difference between both the groups in mean of SBP and DBP. MAP at the interval of T0, T1, T2, T3, T5, T6 (p value >0.05). There was statistical significant difference between both groups in mean of MAP at interval T4. The mean of MAP was higher in group B than group A.

There was increased in MAP after anesthesia induction and decreased at T2 interval.

There was statistically significant differencebetween both the groups at all intervals in the mean of lactate concentration which was higher in group B than group. In our study there was no significant difference between two groups at baseline (p value >0.05) (Ggraph 1)

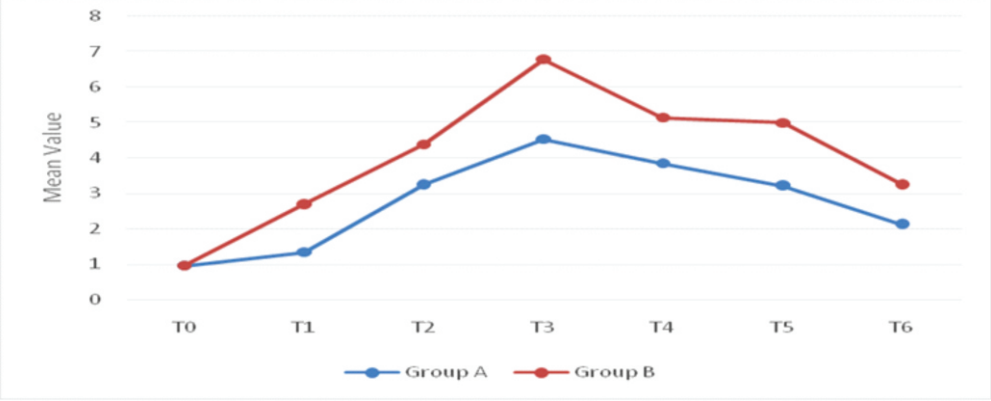
**Table 3: Showing mean heart rate and mean MAP in both the groups**

| | Mean Heart Rate | | | | | Mean Arterial Pressure | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Group A | | Group B | | P Value | Group A | | Group B | | P Value |
| | Mean | SD | Mean | SD | | Mean | SD | Mean | SD | |
| T0 | 82.73 | 12.42 | 82.05 | 16.46 | 0.836 | 83.12 | 13.63 | 78.93 | 14.50 | 0.185 |
| T1 | 110.23 | 21.07 | 119.58 | 22.22 | 0.057 | 103.77 | 16.06 | 107.28 | 19.61 | 0.385 |
| T2 | 85.08 | 12.16 | 84.00 | 12.82 | 0.701 | 80.42 | 14.23 | 83.35 | 16.47 | 0.398 |
| T3 | 95.65 | 11.56 | 98.35 | 13.83 | 0.346 | 81.57 | 14.79 | 85.75 | 15.74 | 0.225 |
| T4 | 77.60 | 10.34 | 73.75 | 15.46 | 0.194 | 74.75 | 10.60 | 82.03 | 18.73 | 0.035 |
| T5 | 80.98 | 10.99 | 84.13 | 11.37 | 0.211 | 79.82 | 10.15 | 81.43 | 11.94 | 0.520 |
| T6 | 81.55 | 13.04 | 81.83 | 16.74 | 0.934 | 85.00 | 9.88 | 80.48 | 12.19 | 0.075 |

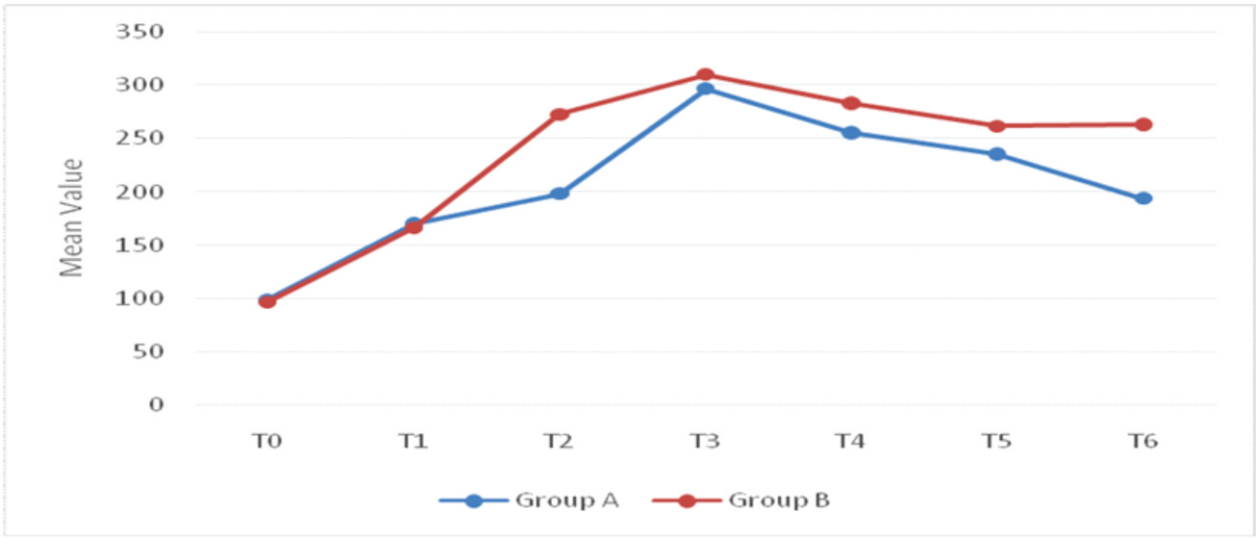
**Table 4: Showing mean $Na^+$ and $HCO_3^-$ distribution in the two groups.**

| | $Na^+$ | | | | | $HCO_3^-$ | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Group A | | Group B | | P Value | Group A | | Group B | | P Value |
| | Mean | SD | Mean | SD | | Mean | SD | Mean | SD | |
| T0 | 138.05 | 2.89 | 136.83 | 2.84 | 0.059 | 22.47 | 1.10 | 22.82 | 1.62 | 0.26 |
| T1 | 138.00 | 2.83 | 138.35 | 3.32 | 0.613 | 22.03 | 0.99 | 22.15 | 0.96 | 0.60 |
| T2 | 137.95 | 3.00 | 138.90 | 3.69 | 0.209 | 21.49 | 0.98 | 21.48 | 0.95 | 0.99 |
| T3 | 137.6 | 3.23 | 137.98 | 2.59 | 0.568 | 20.21 | 1.30 | 19.49 | 1.48 | 0.022 |
| T4 | 138.00 | 3.31 | 137.98 | 3.63 | 0.974 | 20.77 | 1.56 | 20.54 | 1.56 | 0.502 |
| T5 | 137.35 | 3.12 | 136.88 | 2.82 | 0.477 | 21.60 | 1.23 | 20.97 | 1.46 | 0.037 |
| T6 | 137.53 | 2.82 | 137.95 | 2.63 | 0.487 | 22.26 | 1.10 | 21.06 | 1.50 | 0.0001 |

The baseline blood glucose levels were comparable in both of the groups. In present study the mean glucose was higher in group B than group A. This can be explained due to conversion of lactate to bicarbonate and gluconeogenesis. Various studies were in accordance with present study. There was no significant difference



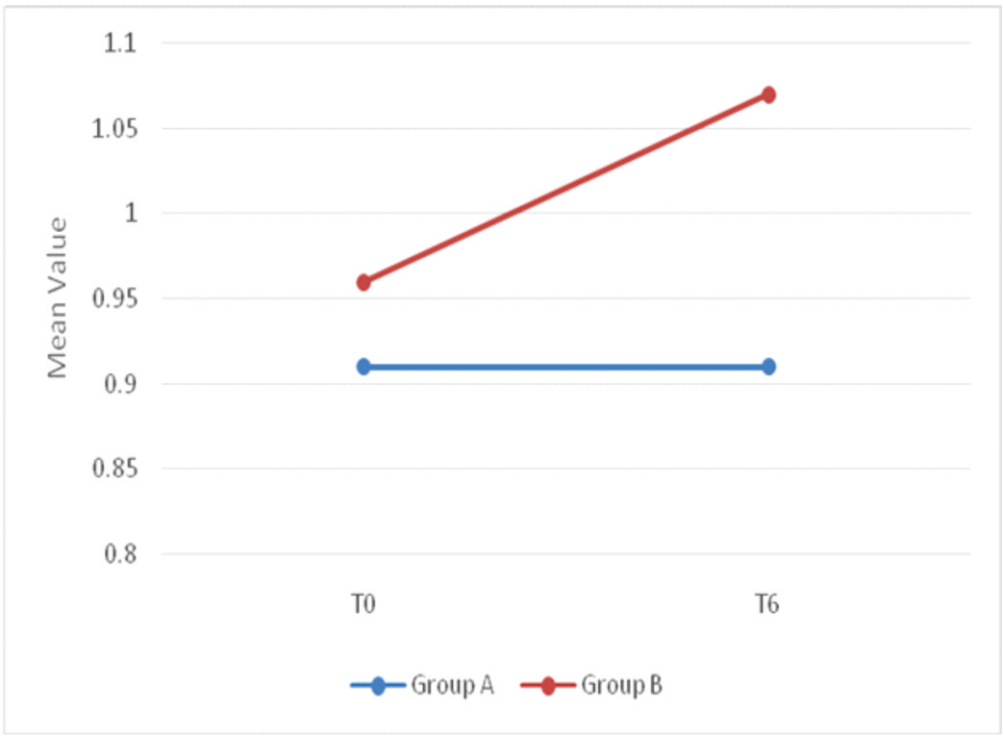

**Graph 1: Showing distribution of mean Lactate levels in two groups.**




**Graph 2: Showing blood Glucose lavels in both groups**

between both the groups at baseline and interval T1 and T3. There was significant difference between group A and group B at interval T2, T4, T5, T6. The mean glucose was higher in group B than group A. (Graph 2) There was significant difference between group A and group B in Serum creatinine and p value was 0.0003 the mean creatinine was higher in group B than group A while base line values were comparable.

There was no significant difference in Sodium (Na+) between two groups (p value>0.05) at baseline and at all intervals.

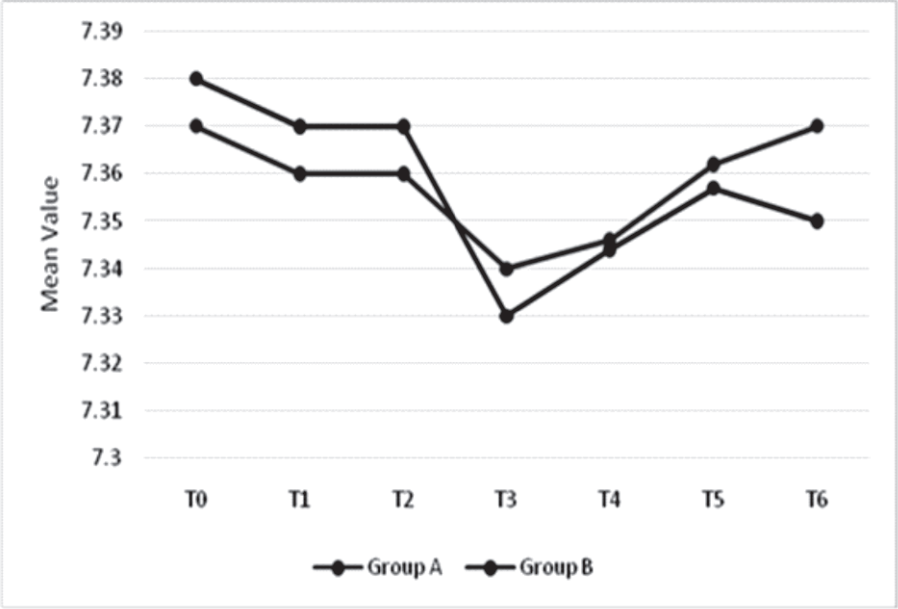



**Graph 3: Showing mean Creatinine levels in both the groups**

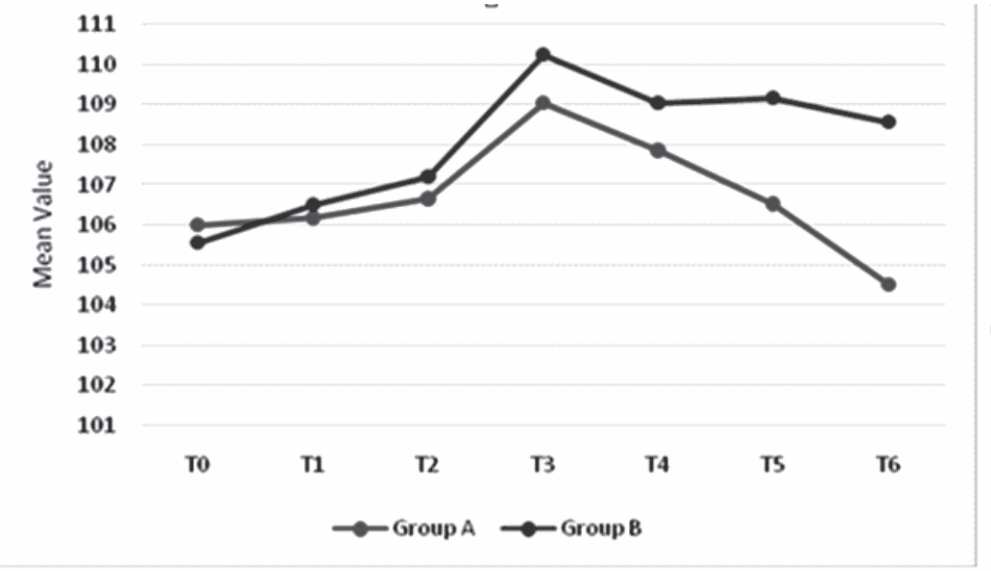
In our study, there was statistically significant difference between both groups in mean **Bicarbonate ($HCO_3^-$)** at interval T3,T5,T6. Mean **$HCO_3^-$** was higher in group A than group B.

We found that the $Cl^-$ was lower in group A than group B at interval T5, T6 this is in accordance with previous studies.

In our study, in the reference of **pH** there was no significant difference between both the groups (p value >0.05) at baseline and interval at T1,T2,T3,T4,T5. (Graph 4). There was significant difference between both the groups at interval T6. The mean pH was higher in group A than group B.




**Graph 4: showing pH distributions in two groups.**




**Graph 5: Showing mean chloride distribution in two groups**

The above Graph shows the mean $Cl^-$ distribution in both the groups. There was no statistical significant difference in mean of $Cl^-$ at the interval T0,T1,T2,T3,T4 between both the groups.

There was statistical significant difference between both the groups at interval T5,T6.

The Mean of $Cl^-$ was higher in group B than group A.

## DISCUSSION

Perioperative intravenous fluid therapy has been a much neglected area of clinical practice[5,6] and suboptimal prescribing has often resulted in morbidity and even mortality[7]. During CPB, mild to severe dysfunction occurs in many organs due to physiological alterations inherent to this technique. As blood is exposed to foreign surfaces, a series of inflammatory reactions that induce changes in capillary permeability are activated. Furthermore, the hemodilution causes by CPB lowers the osmotic pressure, resulting in oedema that may compromise the normal function of many organs[8,9].

A balanced electrolyte solution has the physiological electrolyte pattern of plasma in terms of sodium, potassium, calcium, magnesium, chloride and their relative contributions toward osmolality and achieves a physiological acid-base balance with bicarbonate or metabolizable anions. Infusion of such a balanced solution is devoid of the risk of iatrogenic disruptions except for potential volume overload. A balanced solution should reflect the physiological roles of the sodium, potassium, calcium, and magnesium cations, and also contain chloride and phosphate anions, and, above all, bicarbonate[10].

With this back ground,the present study was performed to compare Balanced Salt Solution and Ringer Lactate fluid administration on plasma electrolytes, acid base status and renal function in cardiac surgery on CPB.

Various studies have been performed to see the effect of balanced salt solution and RL solution on heart rate during at different time intervals. In our study we found that difference in heart rate was not significant among both groups during all time intervals this is in accordance with previous studies conducted by Thomas Stand et al in 2010 who found no significant difference among Hydroxyethyl starch 6% in a balanced electrolyte solution during cardiac surgery[11].

kumar AK, et al in 2017 found that the difference in heart rate was not significant by administration RL and Kabilyte. In our study (Table 3) there was no significant difference between both the groups (p value >0.05). Increased in heart rate after anesthesia induction (T1) in both the groups might be explained as the effect of laryngoscopy and intubation[12].

The presenting study was similar with Anne Kiran Kumar et al in 2017 and Jigar Patel et al in 2016 where they also observed that the MAP was not significantly differ after administration of RL and Kabilytev[12] and priming the bypass machine pump by albumin, Hydroxyethyl starch respectively[13].

In our study (Table 3) there was no significant difference in MAP between both the groups at interval T1,T2,T3,T5,T6 (p value >0.05) except at T4. The mean of MAP was higher in group B than group A.

Boom CE, et al in 2013 and Volta CA, et al in 2013 also observed same results after administration of sodium lactate and balanced fluid during cardiac surgery[14,15].

In reference to $S_PO_2$% the presenting study was comparable with Volta CA, et al in 2013 and Hasan AL per Gurbuz et al in 2013 they also found that the $S_pO_2$% not significantly differ among both the study groups.

There was no significant difference in Sodium ($Na^+$) between both the groups (p value>.05) at baseline and at all intervals. This was in concordance with study of Carlo Alberto et al in 2013[15].

Different studies have been performed to see the effect of balanced salt solution and ringer lactate on chloride ($Cl^-$). In our study we found that the $Cl^-$ was lower in group A than group B at interval T5, T6 this is in accordance with previous studies .

James MFM et al in 2011 also found that the $Cl^-$ was not increased by balanced salt solution administration but increased by RL infusion during surgery[16].

The present study was in concordance with Carlo Alverto volta et al in 2013 who found that there was no hyperchloremia with balanced salt solution in patients undergoing abdominal surgeries but normal saline administration should dilute the bicarbonate concentration of the extracellular space. Based on the Stewart's approach, the decrease of the strong ion difference is mainly the result of the plasmatic increase of chloride (hyperchloremic acidosis)[15].

The presenting study was similar with Bertrand Guidet et al in 2010 they found that dilutional-hyperchloraemic acidosis is a side effect, mainly observed after the administration of large volumes of isotonic saline as a crystalloid. In this particular setting, however, the effect remains moderate and relatively transient (24 to 48 hours), and is minimized with the use of balanced solution[17].

Our study results differ with Kumar AK, et al in 2017, observed higher levels of chloride (RL and sterofundin) compared to plasma, less than that in normal saline but there was no significant difference between the groups in reference to the chloride[12].

There was no significant difference between both the groups at baseline and at interval T1,T2,T4 in mean bicarbonate ($HCO_3^-$).

There was statistically significant difference between both groups in mean bicarbonate ($HCO_3^-$) at interval T3,T5,T6. Mean $HCO_3^-$ was higher in group A than group B.

The present study was in concordance with Roger J Smith et al in 2010, who found that there was reduced incidence of metabolic acidosis with balanced salt solution group[4].

Volta CA, et al in 2013 found similar result as our study that bicarbonate level was higher with balanced salt solution than unbalanced salt solution[15].

Stand T, et al in 2010 observed in their study that The serum chloride level (mmol/L) was lower ($p < 0.05$ at the end of surgery), and arterial pH was higher in the balanced group at all time points except baseline, and base excess was less negative at all time points after baseline ($p< 0.01$)[11].

The presenting study was against the study by Kumar AK, et al in 2017 who found that balanced salt solution and ringer lactate give similar outcome on acid basis status (no change)[12].

In our study in the reference of pH there was no significant difference between both the groups (p value >0.05) at baseline and interval at T1,T2,T3,T4,T5. There was significant difference between both the groups at interval T6. The mean pH was higher in group A than group B.

The present study was in concordance with Volta CA, et al in 2013, they found that there was metabolic acidosis with unbalanced salt solution [15].

Guidet B, et al 2010 found that pH was more with balanced solution then unbalanced solution. And they concluded that dilutional hyperchloraemic acidosis is a side effect, mainly observed after the administration of large volumes of isotonic saline as a crystalloid. In this particular setting, however, the effect remains moderate and relatively transient (24 to 48 hours), and is minimized with the use of colloids[17].

Kumar AK, et al in 2017 found that pH was more with balanced solution than and unbalanced solution and also lactate and glucose level was more with RL solution[12].

The present study (graph 1) was in accordance with Volta CA, et al in 2013, and they found that the lactate level was more with RL Solution then balanced salt solution[15].

In our study there was no significant difference between two groups at baseline (p value >0.05). There was statistically significant difference between both the groups at intervals T1, T2, T3, T4, T5 and T6 the mean of lactate concentration was higher in group B than group A.

The baseline blood glucose was comparable in both of the groups. In present study the mean glucose was higher in group B than group A. This can be explained due to conversion of lactate to bicarbonate and gluconeogenesis.

Various studies were in accordance with present study.

Kumar AK, et al in 2017, found similar results that the glucose level was more with RL solution[7].

The present study (graph 2) was consistent with Carlo Alverto Volta et al in 2013, as they found that the glucose level was more with RL Solution than balanced salt solution group[15].

There was significant difference between group A and group B in Serum creatinine and p value was 0.0003 the mean creatinine was higher in group B than group A.

The present study was in concordance with SM Alvani, et al 2012 and they also found that kidney function was better in the short term in the HES group than in the other two groups (RL and Gelatin Group)[18].

Carlo Alverto Voltaet et al in 2013 also observed that the use of balanced solutions was responsible of less

alteration of kidney function and it might be associated with an early anti-inflammatory mechanisms triggering.

The present study was against with Hasan Alper Gurbuz et al in 2013. And they did not document any difference between HES and crystalloid solutions used for CPB priming regarding postoperative outcomes like postoperative bleeding, renal functions and the use of blood and FFP[6].

Limitations of the study This study had some limitations including the absence of the data expressing cardiac contractility after BSS or RL infusion and measurement of extra vascular lung water. We were unable to measure due to lack of suitable monitors.

## CONCLUSION

The BSS (Kabilyte) is better fluid than RL solution due to reduced incidence of hyperchloremic metabolic acidosis and less increased level of serum glucose and lactate. Renal functions are better preserved in BSS group.

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## ORIGINAL ARTICLE

# Assessment of Relationship of Coronary Artery Disease Severity and 30 Days Outcome in Patients with Non-ST Elevation Myocardial Infarction with ST Segment Elevation and T Wave Change in Lead aVR

**Anamika Gupta*, Balbir Singh Pachar**, Mamta Sharma***, Ana Pachar****, Anoop Jain*****, Shekhar Kunal******, Kusum Gaur*******


## ABSTRACT

**Objectives:** ST elevation in lead aVR (STEaVR) is considered to be a predictor of left main/ or triple vessel coronary artery disease (CAD) in patients with Non- ST Elevation Myocardial Infarction (NSTEMI). STEaVR and positive T wave in aVR have been shown to be related with increased mortality in patients with NSTEMI. The aim of this study was to investigate the association of STE aVR and ratio between ST segment in aVR and T wave amplitude in aVR (STaVR/TAaVR) with left main/triple vessel disease (LM/TVD), Syntax Score (SS) and 30 days major adverse cardiac events (MACE).

**Methods:** 402 consecutive NSTEMI patients undergoing coronary angiography were included in this prospective observational study. Patients were divided into two groups, based on ST segment elevation (defined as $\geqslant$0.5mm) in lead aVR. The ratio using absolute values of STaVR and TAaVR were calculated- Ratio 1: STaVR/TAaVR and Ratio 2: TAaVR/STaVR. Syntax score was calculated using Coronary angiography (CAG) images. Study variables were compared between two groups.

**Results:** NSTEMI patients with STEaVR had higher rates of LM/TVD (39.5% vs 26%, p=0.011), and higher value of SS (17.8 vs 14.4, P=0.001). A significant positive correlation was observed between SS and STEaVR (r=0.21, P=0.001), SS and TAaVR (r=0.36, p=0.001), SS and ratio 1 (STaVR/TAaVR) (r=0.28, p=0.001) as well as ratio 1 and MACE (r=0.23, p=0.001).

**Conclusions:** NSTEMI patients with ST elevation in aVR have significantly higher rate of LM/TVD. STEaVR and positive T wave in aVR correlates with Syntax Score. The ratio (STaVR/TAaVR) may be useful to predict severity of CAD in NSTEMI.


**Keywords:** Coronary artery disease; lead aVR; major adverse cardiovascular events; non ST elevation myocardial infarction; Syntax score

## INTRODUCTION

Cardiovascular diseases are a major cause of morbidity as well as frequent hospitalizations and account for nearly one-third of all the deaths[1]. Non-ST elevation acute coronary syndromes (NSTE-ACS), comprises upto 60-70% of ACS patients having varying degrees of atherosclerosis. The prognosis of these patients tends to vary as most of them are managed conservatively followed up with cardiac enzymes without early invasive intervention in absence of chest pain[2-4]. Non-specific electrocardiogram (ECG) findings such as ST segment depression, negative T waves in the precordial leads, ST segment elevation in lead aVR (STEaVR) and positive T waves in lead aVR are detected in approximately 60-70% of NSTE-ACS patients. These ECG changes are often shown to have a correlation with the severity of coronary artery disease (CAD)[5,6]. Multiple studies have revealed that STEaVR predicted left main involvement or (LM/TVD) in NSTE ACS[7,8]. Several studies have shown an increased mortality in NSTE-ACS patients with STEaVR as compared to those without ST elevation in

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aVR[9,10], however, this finding has not been confirmed in all studies[11].

The Synergy between percutaneous coronary intervention (PCI) with Taxus and CABG (SYNTAX) Score (SS) is a comprehensive scoring method used to show the severity of CAD and predicting short term and long term prognosis in NSTEMI[12]. Few studies have found an association between mortality and T wave amplitude in lead aVR (TAaVR) in the patients with STEMI and NSTEMI[13,14]. Although it has been found that positive TAaVR and elevated STaVR affect the prognosis adversely in patients with NSTEMI, there is no concluding study evaluating their role in assessment of CAD severity[15]. In addition, the role of a positive T wave for determining the extent of coronary stenosis is not well known. Early identification of patients with severe CAD is an important factor in the prognosis and selection of the optimal treatment strategy in patients with NSTEMI as high risk may benefit from early invasive therapies like (PCI) or coronary artery bypass graft (CABG). Specific ECG findings may be useful when added to risk score systems which predict prognosis such as GRACE (Global Registry of Acute Coronary Events) and TIMI (Thrombolysis in Myocardial Ischemia), and predict the severity of CAD disease in NSTEMI[16,17].

Previously described scores predict poor prognosis but not necessarily correlated with LM/TVD. Regarding these facts, we investigated the role of ST segment elevation in aVR (STEaVR) or ratio between ST segment in aVR and T wave amplitude in aVR (STaVR/TAaVR) with CAD severity by observing their association with left main(LM)/ or triple vessel coronary artery disease and SYNTAX Score. This study also aimed to find an association between STEaVR and STaVR/TAaVR ratio with one-month major adverse cardiac events (MACE) defined as death, recurrent myocardial infarction, stroke, major bleeding and target vessel revascularization.

## MATERIALS AND METHOD

**Study design and patient population:** This was a single centre, prospective observational study performed at the Department of Cardiology at a tertiary care medical center from April 2018 to Jan 2020. The study complied with the ethical principles stated in the Declaration of Helsinki and was approved by institutional ethical committee. Written informed consent was obtained from each participant. A total of 402 consecutive patients (age >18 years) with recently diagnosed NSTEMI and undergoing coronary angiogram were included. A diagnosis of NSTEMI was based on presence of symptoms suggestive of acute coronary syndrome along with an elevated cardiac troponin-T exceeding the 99th percentile of normal reference limit without ST segment elevation[18]. Patients having an ECG finding on presentation indicative of STEMI, with pre existing ECG abnormalities affecting ST-T changes such as left or right bundle branch block, left ventricular hypertrophy, ventricular pacing, ventricular pre-excitation, non-ischemic cardiomyopathy, acute pulmonary embolism, severe valvular heart disease and aortic dissection were excluded. Patients who had recent (<6 months) PCI or prior CABG, severe renal function disorders (estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 $m^2$), hepatic function disorder or having a clear alternate cause for the symptoms, active or chronic inflammatory conditions were excluded.

**Study procedures and laboratory analysis:** Demographic characteristics, medical history, presenting symptoms, CAD risk factors, physical examination, duration of pre-hospital delay, biochemical and ECG findings, hospital stay and 30 day outcome data were collected. Cardiac biomarkers including cardiac Troponin-T was analysed using radiometer AQT90 flex analyzer and serum Creatine Kinase Myocardial Band isoenzyme (CK-MB) was measured using autoanalyzer. Renal function test, lipid profile, complete blood count, differential leucocyte count, platelet count were obtained using standard biochemical techniques using separate autoanalyzer.

A 12-lead surface ECG (rate 25 mm/s, standard 1mV/10mm) was recorded within 10 minutes of presentation in emergency, or whenever patient deteriorated clinically or complained of chest pain. At least three ECGs were obtained during the period of hospitalization. ST segment elevation was defined as ST segment elevation $\geqslant$ 0.05 mV (0.5mm) in the limb leads and ST segment elevation $\geqslant$ 0.1 mV (1mm) in the precordial leads using the preceding TP segment as a baseline. T wave amplitude in aVR (TAaVR) was measured depending on the PR segment in lead aVR. Negative and positive numeric values according to below or above location of ST segment or T wave in lead aVR were recorded using digital caliper. The absolute values of

STaVR and TAaVR were obtained and the following ratios were calculated- ratio 1: STaVR/TAaVR and ratio 2: TAaVR/STaVR.

Coronary angiography (CAG) was performed through femoral or radial artery access (Judkin's technique), using manual injection of low osmolar, non-ionic contrast (Iohexol) by treating physician after obtaining a written informed consent. Stenosis diameter ⩾ 70% with quantitative angiography was accepted as significant. The Syntax score (SS) was calculated by including the vessels with a diameter larger than 1.5mm and a stenosis over 50% from CAG images. All patients received aspirin, clopidogrel or tecagrelor, heparin or enoxaparin, beta blocker, angiotensin convertase enzyme (ACE) inhibitor according to the disease profile as per treatment guidelines for NSTEMI[19,20]. After one month of the index event, data regarding major adverse cardiac events (MACE) were obtained during outpatient clinic visit or telephonically, which were defined as a composite of all-cause mortality, cardiac death, stroke, non-fatal MI, target vessel revascularization (TVR), major bleeding according to the Academic Research Consortium definition[21]. Cardiac death was defined as death resulting from any cardiac-related causes. Non-fatal myocardial reinfarction was defined as increased cardiac biomarkers, characteristic dynamic and evolving electrocardiographic changes and prolonged chest discomfort), or emergency PCI. TLR was defined as repeat revascularization caused by ⩾ 50% stenosis within the stent or within 5 mm proximal or distal to the stent. Major bleeding was defined as bleeding requiring transfusion or surgery, decrease in hemoglobin of ⩾5 g/dl, and intracranial hemorrhage.

**Statistical analysis:** The study participants were divided into two groups based on presence of ST elevation in aVR: Group 1 including NSTEMI patients with ST elevation in Lead aVR and group 2 including NSTEMI patients without ST elevation in aVR. The study variables were divided as categorical and continuous variables. The Continuous data were expressed in mean and standard deviation and unpaired 't' test was applied to compare the variables. The categorical data were expressed in numbers, proportion and percentages, and chi square test or Fisher exact test was applied to compare. Pearson correlation coefficients were used find out correlation between Syntax score and various variables. Linear regression analysis was done for major cardiac indices and regression line with $R^2$ was found. ROC curve was drawn between true positive rate (Sensitivity) and false positive rate (1-Specificity) of LM/TVD to find out the Area under Curve (AUC). The statistical analyses were performed using the SPSS 24.0 (SPSS Inc., Chicago, IL) software in windows operating system. p value <0.05 was considered significant.

## RESULTS

A total number of 402 patients were included in this study. The mean age was 56.38±9.53 years, ranging from 31 to 76 years and 59.2% of the patients were males. Demographic data of the two groups are presented in Table 1. A total of 119 patients (29.6%) had ST elevation in aVR ⩾ 0.5 mm while 78 patients (19.4%) had positive T wave in aVR.

**Patient characteristics:** In the study groups, no significant differences were found regarding the age, history of smoking, diabetic status, time of onset of ischemic symptoms, hemoglobin, high-density lipoprotein (HDL) and triglyceride levels. Patients in group 1 had statistically significant higher BMI levels, higher systolic and diastolic blood pressure levels, higher levels of creatinine, total cholesterol and low density lipoprotein (LDL). Group 1 patients also had significantly higher levels of Troponin-T and CK-MB. Patients with ST elevation in aVR had significantly lower levels of LV ejection fraction.

### Coronary angiographic findings and cardiac procedures during hospitalization

Coronary angiography was performed in all recruited patients. Coronary angiographic data, depicted in table 2, revealed that almost half of the patients (44.8%) had single-artery disease, which did not differ between the two groups. However, Group1 patients had significantly higher rate of LAD involvement (68.9% vs 59%; p=0.001) as well as higher proportion of LM/TVD as compared to Group 2 (39.5% vs 26%; p=0.011). While plotting receiver operator curve (ROC) for STEaVR ⩾ 0.5 mm, the sensitivity for LM/TVD came out to be 28.9% and specificity came out to be 83.9% (Figure1). Also, patients in Group 1 had significantly higher mean Syntax score (SS) as compared to those in Group 2 (17.8 vs 14.4; p<0.001). In our study, there was no difference in the number of patients undergoing PCI or CABG between the two groups. In the correlation analysis, a statistically significant positive correlation was observed between ST

elevation in lead aVR and SS (r=0.21, p=0.001) (Figure 2), T wave in aVR with SS (r=0.36, p=0.001) as well as Ratio1 (STaVR/TAaVR) and SS (r=0.28, P=0.001) (Figure 3).

**Predictors of 30 day outcome:** Total number of patients who could be followed up was 368. A total of 67 patients (16.6%) patients had major adverse cardiovascular events (MACE) at one month follow up. There was a trend towards higher rate of MACE in Group 1, however the differences did not reach a statistical significance. We observed a statistically significant positive correlation between MACE and SS (r=0.32, P=0.001), as well as MACE and ratio 1 (r=0.23, P=0.001).

## DISCUSSION

The present study showed that 29.6% of patients with NSTEMI had ST-segment elevation in lead aVR. The main finding of our study is the significant association of ST elevation in lead aVR as well as ratio 1 (STaVR/TAaVR) with CAD severity determined by left main/ triple vessel disease (LM/TVD) and syntax score on coronary angiography. In addition, this is the first study in Indian population to report that the NSTEMI patients with ST elevation in lead aVR had higher rates of LM/TVD and Left anterior descending (LAD) artery involvement. The possible mechanisms of such associations may be transmural ischemia of the basal interventricular septum or circumferential subendocardial ischemia of the left ventricle owing to significant disease in left main coronary artery or proximal left anterior descending artery. In such case, the ST-segment vector in the frontal plane points in a superior direction leading to ST-segment elevation in lead aVR[22-24].

The higher prevalence of ST-segment elevation in aVR (29.6%) observed in our study was comparable to that reported in prior studies (26-32.3%)[8,10]. Our study found a significantly higher rate of LM/TVD in patients with STEaVR as compared to patients without STEaVR (39.5% vs 26%, p=0.011). Misumida et al., previously in a retrospective analysis of 379 NSTE-ACS patients, reported that subjects with ST elevation in aVR had a significantly higher rate of LM/ triple vessel disease than those without STEaVR (39% vs 18%, respectively, p <0.001)[8]. In an another retrospective analysis of 1042 patients with NSTE-ACS, Barrabés et al., documented that patients having ST elevation in lead aVR had a higher prevalence of LM/ triple vessel disease with an increased mortality as compared to patients without STE in aVR[10]. In addition, Kosuge et al. showed that NSTE-ACS (n=333) patients with ST elevation (>0.05 mV) in aVR had an increased risk of LM/ TVD and death or reinfarction at 90 days[25]. Similarly, Szymanski et al. demonstrated that all cause mortality within 30 days was higher among the patients with ST elevation in aVR and is based on its relationship with multivessel disease and left main coronary artery obstruction[26]. We found that NSTEMI patients with STEaVR $\geqslant$ 0.5mm had higher proportion of MACE at 30 day, however it did not achieve statistical significance. Yan et al. also observed that ST elevation in lead aVR $\geqslant$ 1 mV was not an independent predictor of in-hospital and 6-month mortality after adjustment by GRACE risk score[11]. Thus, in agreement with previous studies, our study confirmed the role of STEaVR in predicting LM/TVD in NSTEMI patients with a lower sensitivity of 28.9% but a good specificity of 83.9%, as compared to prior study, where STEaVR identified LM/TVD with a sensitivity of 78% and specificity of 86%[25].

Syntax score is widely used in the evaluation of angiographic severity and extent of coronary lesions, and has been shown to predict mortality in addition to its role in the decision-making process of interventional procedure[27]. In our study, we observed that patients with STEaVR had significantly higher value of SS (17.8±9.8 vs 14.4±8.9, p=0.001) as compared to those without STEaVR. We also found a significant positive correlation between STEaVR and SS (r=0.21, p=0.001).

Our study also observed a statistically significant correlation of T wave amplitude in aVR with Syntax score (r=0.36, p=0.001). However, we did not observe any correlation between T wave amplitude and 30 day MACE. T wave which represents the repolarization of ventricles can be inverted due to disruption of normal physiologic repolarization of cardiac myocytes. Inversion of T wave in lead aVR manifests as a positive T wave[28]. Separham et al. demonstrated that positive T wave in lead aVR was an independent predictor of LM/ TVD however; it was not an independent predictor of MACE in patients with NSTEMI[14]. In a recent study, Icen et al. determined the amplitude of T wave and ST segment deviation in lead aVR 306 patients with NSTEMI and calculated a ratio by

dividing the variable with larger absolute value by other variable with a smaller absolute value in lead aVR. They showed that this ratio was strongly and independently associated with Syntax Score[15]. We analyzed a proportional combination of absolute values of STaVR and TAaVR ratio as a whole and found a significant association of ratio 1 (STaVR/ TAaVR) with SS (r=0.28, p=0.001) as well as MACE (r=0.23, p=0.001).

The strengths of our study were that this was a prospective study including 402 patients of NSTEMI with a one month follow up to observe MACE. We excluded patients with posterior (inferolateral) wall MI presenting with ST-segment depression in V1–V4, which is equivalent of STEMI. Serial ECGs were done to properly evaluate the patients with NSTEMI. Limitations of our study included that it was single center study with a relatively small sample size and a limited duration of follow-up. Multicentered and controlled studies with large sample size and long term follow up, are needed to support the strong correlation and independent determination of these ECG variables.

## CONCLUSION

ST segment elevation in lead aVR on surface ECG which is a non-invasive, simple, economical tool may predict Left Main/ triple vessel diseases in NSTEMI patients. ST elevation in aVR and positive T wave in aVR correlates well with syntax score which is a marker of coronary artery disease severity. The ratio (STaVR/TAaVR) may be more useful to predict severity of CAD and short term MACE in patients with NSTEMI, if added to risk scoring methods and rapid decisions for early intervention and revascularization could be taken in such patients.

**Table 1: Comparison of demographic, clinical and laboratory findings of study participants between the two groups**

| | NSTEMI patients with ST Elevation in aVR (STEaVR) GROUP 1( N=119) | NSTEMI patients without ST Elevation in aVR (STEaVR) GROUP 2 (N=283) | p Value |
|---|---|---|---|
| Age (years ) | 56.7±8.9 | 56.3±9.8 | 0.7(NS) |
| Males | 73 (61.3%) | 165 (58.3%) | 0.32 (NS) |
| Females | 46 (38.7%) | 118 (41.7%) | 0.32 (NS) |
| BMI (kg/m2) | 24.7± 4.8 | 23.8± 5.4 | **0.003(S)** |
| Smoker | 38 (31.9%) | 104 (36.7%) | 0.14 (NS) |
| Hypertension | 57 (47.8%) | 87 (30.7%) | **0.002(S)** |
| Diabetes | 50 (42%) | 101 (35.6%) | 0.27 (NS) |
| Dyslipidemia | 47 (39.4%) | 79 (27.9%) | **0.03 (S)** |
| Family history | 36 (30.2%) | 80 (28.2%) | 0.79 (NS) |
| H/O CAD | 24 (20.1%) | 38 (13.4%) | 0.11 (NS) |
| Time of onset(hours) | 9.39± 5.25 | 9.12± 4.8 | 0.22 (NS) |
| Troponin- T(ug/L) | 0.23±0.24 | 0.15±0.28 | **<0.001 (S)** |
| CK-MB(IU/L) | 66.07±16.02 | 53.08±10.6 | **<0.001 (S)** |

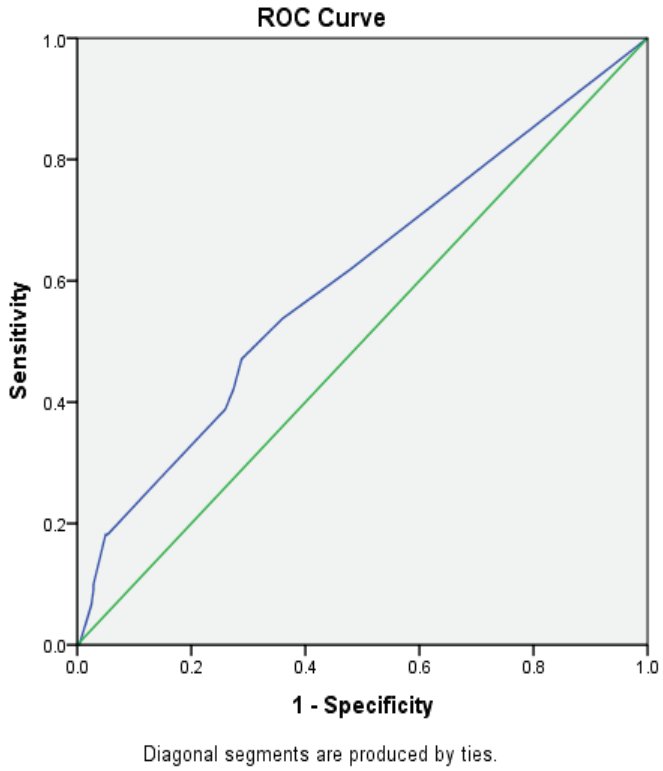
| | NSTEMI patients with ST Elevation in aVR (STEaVR) GROUP 1( N=119) | NSTEMI patients without ST Elevation in aVR (STEaVR) GROUP 2 (N=283) | p Value |
|---|---|---|---|
| SBP (mm of Hg) | 138.4±21.8 | 132.5±20.4 | **0.009 (S)** |
| DBP (mm of Hg) | 85.3±12.3 | 81.4±11 | **0.002 (S)** |
| Creatinine (mg/dl) | 1.19±0.3 | 1.1±0.3 | **0.006(S)** |
| Total Cholesterol (mg/dl) | 182.9±41.9 | 173.6±36.6 | **0.027 (S)** |
| LDL (mg/dl) | 112.1±36.7 | 103.9±36.9 | **0.042 (S)** |
| LVEF (%) | 52.98±6.08 | 54.4±5.7 | **0.026(S)** |
| RATIO1 : STaVR / TAaVR | 0.35±0.23 | 0.04±0.12 | **<0.001 (S)** |
| RATIO 2 : TAaVR/STaVR | 3.46±2.07 | 7.57±13 | **<0.001 (S)** |

BMI= Body mas index, CAD= coronary artery disease, CK-MB= Creatine Kinase Myocardial Band isoenzyme, DBP= Diastolic blood pressure, HDL= High density lipoprotein, LDL= Low density lipoprotein LVEF= left ventricular ejection fraction, NSTEMI= Non ST elevation myocardial infarction, SBP= Systolic blood pressure, STaVR= ST segment change in lead aVR, TAaVR= T wave amplitude in lead aVR.

**Table 2: Comparison of coronary angiography findings and outcome of study participants between the two groups**

| | NSTEMI patients with ST Elevation in aVR GROUP 1( N=119) | NSTEMI patients without ST Elevation in aVR GROUP 2 (N=283) | p VALUE |
|---|---|---|---|
| SVD | 46 (38.6%) | 134 (47.3%) | 0.12 (NS) |
| DVD | 36 (30.2%) | 63 (22.2%) | 0.09 (NS) |
| LM /LM+TVD | 47 (39.5%) | 74 (26%) | **0.011 (S)** |
| Insignificant CAD | 14 (11.7%) | 33 (11.7%) | 0.9 (NS) |
| LAD | 82 ( 68.9% ) | 167 ( 59% ) | **<0.001 (S)** |
| LCX | 57 ( 47.8% ) | 121 ( 42.7% ) | 0.40 |
| RCA | 50 ( 42% ) | 128 ( 45.2% ) | 0.63 |
| LM | 42 ( 35.2% ) | 52 ( 18.3% ) | **<0.001 (S)** |
| Syntax score (SS) | 17.79±9.78 | 14.43±8.9 | **<0.001 (S)** |
| PCI | 63 ( 52.9% ) | 181 ( 63.9% ) | 0.06 (NS) |
| CABG | 17 ( 14.2% ) | 28 ( 9.9% ) | 0.27 (NS) |
| MACE | 24 ( 20.2% ) | 43 ( 15.2% ) | 0.28 (NS) |

CAD= coronary artery disease, CABG= coronary artery bypass graft, DVD = double vessel disease, LAD=Left anterior descending, LCX= left circumflex, LM= left main, MACE= major adverse cardiovascular events, PCI= percutaneous coronary intervention, RCA= Right coronary artery, SVD= single vessel disease, TVD= Triple vessel disease.




| | STEaVR ⩾5mm |
|---|---|
| Sensitivity | 28.9% |
| Specificity | 83.9% |
| AUC | 0.602 |
| 95% CI | 0.54-0.66 |

**Figure 1: ROC curve for ST elevation in aVR for predition of Left main/Triple vessel disease on coronary angiography.**

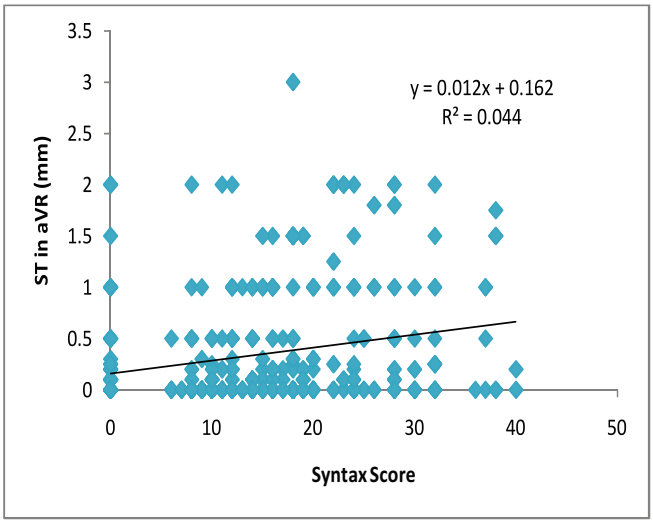



**Figure 2: Correlation of Syntax score with ST elevation in lead aVR.**

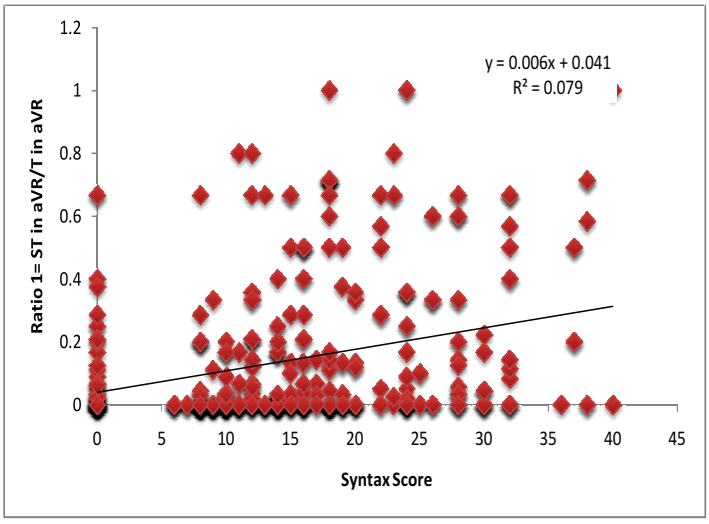



**Figure 3: Correlation of Syntax score with ratio 1 (STaVR/TAaVR).**

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## REVIEW ARTICLE

# Living with the Virus: Considerations & Challenges in Restarting "New Normal" Surgical Practice

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## ABSTRACT

COVID -19 disease has taken a toll on the healthcare system and the number of cases is increasing at alarming rates. The long incubation period, asymptomatic patients, the aggressive spread of the virus, and lack of definitive treatment are the main reasons, why the infection could not be contained so far.The intended goals of this review are to provide logical & rationale management of patients in the present time, the judicial utilization of the available resources (manpower, infrastructure, safety gears) and preventing or minimizing the risk of infection to the public, patients, co-patients and healthcare workers (HCW's), as well as to explore the requirements for restarting the new normal hospital practice. HCW's need to take precautions assuming all patients as COVID positive unless proven otherwise. Patients should be categorized based on the COVID status and further based on the urgency of surgery into acute, sub-acute & chronic cases. The review & recommendations can be used to reduce the risk of exposure from human to human as well as in planning the strategy on how to restart a safe practice in surgical specialties.

**Key words:** COVID-19, Corona virus, pandemic, Surgery, recommendations, protocols, Management, restart practice

## INTRODUCTION

The severe acute respiratory syndrome virus 2 (SARS-CoV-2) has led to the global pandemic of the coronavirus disease (COVID-19)[1]. As of June 16, 2020, there have been 7,941,791 confirmed cases and 434,796 deaths reported to the WHO[2]. The virus has a high reproductive number (R0) of 3 to 4, which means that one case can potentially infect upto 4 cases[3]. The trends from China & Italy show that we will have to live with the virus for a significantly longer duration. This means that all the healthcare systems will have to be back in pace as there has been an immense pending patient demand. Our health care organizations, physicians and surgeons must be prepared to meet this demand.

Novel infection explains the absence of immunity, an effective anti-viral drug and vaccinations against it. Health care workers (HCW) are exposed to patients who are moderate to severely afflicted[4]. Further invasive procedures leading to aerosol generation such as intubation or endoscopy further predispose health care professionals (Figure 1). Prolonged working hours, inappropriate diet, and certain comorbid conditions further compromise the immunity. A recent systematic review performed using the available literature suggested that the overall proportion of HCW who were SARS - CoV -2 positive among all COVID -19 patients was nearly ten percent. Importantly, the same review found that more than half of the COVID -19 positive HCW reported that they had contact with COVID -19 positive patients in healthcare settings[5]. Therefore, it is imperative that HCW take the utmost care when performing their duties. Furthermore, it is prudent to form guidelines for rationale management of positive & suspected patients requiring outpatient services, emergency procedures and surgeries so that the HCW does not succumb to the infection. We hereby present a comprehensive review of the various guidelines that have been issued. The aim of this review is to analyze evidence and discuss strategies that when adopted can reduce the transmission of the virus to health care workers dealing with confirmed or suspected COVID-19 cases.

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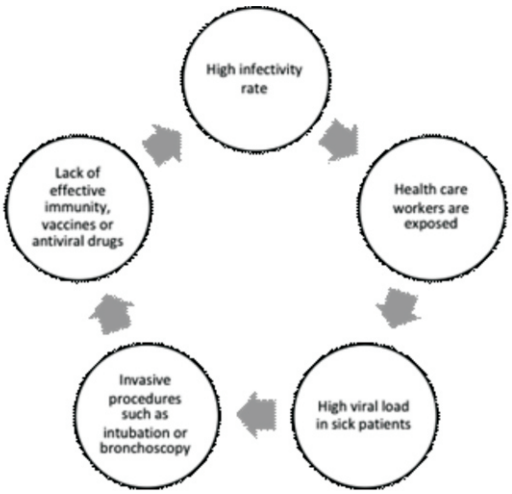


**Figure 1: Vicious cycle leading to increased risk of COVID-19 infection in health care worker**

**Structure and Pathophysiology of COVID-19:** SARS-CoV-2, is an enveloped non-segmented single-stranded positive-sense RNA virus. The structure of the virus includes four essential structural proteins, including spike (S) glycoprotein, small envelope (E) protein, matrix (M) protein, and nucleocapsid (N) protein and 16 non-structure proteins (NSPs)[6,7].

Pathophysiology and virulence mechanisms of COVIDmay be linked to the structure of non-structural proteins (NSPs) and structural proteins. As far as the function of the structural proteins is concerned, the envelope has a crucial role in virus pathogenicity as it promotes viral assembly and release. However, the exact pathophysiological mechanisms are still not clear as no animal model exists and most of the research has been carried out on Vero E6 cells.

**Virus host interactions:** Two host proteins play a major role for cell entry and replication of the virus: i) angiotensin-converting enzyme 2 (ACE2) which serves as the SARS-CoV entry receptor by binding to the S1 spike and ii) the endosomal compartment transmembrane protease serine 2 (TMPRSS2) which causes priming/cleavage of the S1 spike glycoprotein enabling the fusion of the viral envelope with the endosomal compartment. After this, the virus replicates and releases multiple copies in the host[8]. ACE2 receptor is found on alveolar cells of the lung epithelium (most abundant in type II alveolar cells), glandular cells of the gastric, duodenal and rectal epithelium, heart and peripheral nerves. Non ACE2 pathways for virus infection cannot be excluded and this is still an extensive area of research.

Having entered the host, the interaction of the virus with the host cell triggers the immune system. Macrophages release numerous cytokines in response, particularly IL-6. Other cytokines and chemokines include IL-1, IL-2, IL4, IL-7, IL-10, IL-12, IL-13, IL-17, GCSF, macrophage colony-stimulating factor (MCSF), IP-10, MCP-1, MIP-1α, hepatocyte growth factor (HGF), IFN-γ and TNF-α which might lead to a cascade representing an overzealous and overwhelmed immune response. This is termed as the macrophage activation syndrome/cytokine storm which is a form of secondary hemophagocytes and potentially a fatal immune response[9]. Inflammatory response signaling pathways include recruiting adaptors such as IFN-β (TRIF), mitochondrial antiviral-signaling protein (MAVS) and stimulator of interferon genes protein (STING) trigger downstream cascades molecules, involving adaptor molecule My D88 and lead to the activation of the transcription factor nuclear factor-κB (NFκB) and interferon regulatory factor 3 (IRF3)**[10].** Some patients can even develop a coagulopathy meeting the criteria of disseminated intravascular coagulation (DIC)[11].

**Preparedness for Coronavirus disease 2019 (COVID-19) in the outpatient clinics and day care procedures**

**Outdoor practices to reduce spread of COVID-19 infection:** Each institute should draft a policy on how to deal with patients in outdoor, treatment policies, triage areas[12]. All health care professionals working in the hospital should be updated and educated about the same[13].

Healthcare facility areas should be well ventilated[14]. In settings where windows cannot be opened and where ventilation is in a closed circuit, high-efficiency particulate air (HEPA) filters should be used for recycling the air. The common areas such as the reception, waiting rooms, procedure rooms, and recovery rooms should be first cleaned with neutral detergent followed by decontamination of surfaces with disinfectants effective against viruses. These may comprise of an appropriately diluted solution of household bleach or 70% ethanol. It is also imperative to clean the wash basins, toilets, and bathrooms. The use of single-use disposable cleaning equipment (e.g. disposable towels) is recommended. If unavailable, then the cleaning material (cloth, sponge

etc.) should be placed in an appropriate disinfectant solution else it should be discarded and not reused[14].

Chairs in waiting areas should be kept far apart. Magazines, information booklets, and other materials should be removed from the waiting area. Appropriate signages about the symptoms of COVID-19, what should be done, and what should not be done should be put at points with easy visibility for the patient. Sanitizers, wash basin with soap and appropriate waste disposal bins should be made available. Equipment such as blood pressure cuffs and stethoscopes should be sanitized in between patients.

Social distancing, hand sanitization and use of face masks should be mandatory to reduce cross-infection. Crowd control is required and appropriate spacing between various patients is needed. Sanitization of the outpatient area and innocuous appearing areas in the outdoors, registration counters, and pharmacy are required. Training of doctors, nursing staff, and ward help in terms of disease symptoms, measures to prevent, donning, and doffing of personal protective equipment (PPE) should be done[12,13]. Areas should be designated for donning and doffing of PPE, dispensers for sanitizers, wash basins with soap, and dustbins.

Patients with acute onset of respiratory symptoms including cough, fever, and respiratory difficulty should inform beforehand about them. A separate counter should be prepared to deal with these patients with acute respiratory infection (ARI) and severe acute respiratory illness (SARI)[15]. The health care professionals dealing with these patients should wear personal protective equipment. Patients with non-urgent symptoms should have their appointments rescheduled.

Patients upon arrival should first undergo screening whether symptoms are present. Those with symptoms of ALI or SARI should be triaged to the COVID-19 desk. If a patient is COVID suspect patient, then he/she should either be admitted to a COVID ward or shifted to a COVID dedicated hospital. The patients attending the hospitals can be classified into three as per Table 1.

**Table 1: Three cohorts of cases in the current covid era**

| COHORT | Symptoms | Laboratory features |
|---|---|---|
| A | Asymptomatic for COVID symptoms | RT-PCR negative.<br>Blood Counts or CxR not typical of COVID infection<br>No clinical or history evidence(Hotspot inhabitant) suggestive of COVID disease |
| B | Suspected for COVID disease | RT-PCR report awaited<br>RT-PCR report Negative but the patient appears clinically suspicious of Covid infection<br>Hotspot inhabitant<br>Blood Counts or CxR typical of Covid infection |
| C | Infected Patients | RT-PCR Positive |

A check team should be present in every outdoor clinic to ensure that the aforesaid measures such as face mask by everyone, availability of sanitizers at designated areas, distancing at counters, no spitting, and waste disposal in bins are implemented by one and all.

Transit wards or suspect areas should be designated in each hospital while admitting COVID suspects. Health care professionals taking care of these patients should be provided with proper PPE. Sanitization and cleaning of these wards are essential.

Strict measures should be taken to limit the entry of visitors and attendants into the healthcare facilities. Specifically, visitors should strongly be discouraged from visiting patients who are at high risk for severe illness from COVID-19. A separate visitor entrance should be designated and visitors should only be allowed when

necessary. All visitors should be screened for COVID symptoms and fevers and those who are found to have fever or symptoms of acute respiratory illness should be immediately asked to leave the facility and seek care, as needed[16].

**Role of Telemedicine:** Telemedicine would play a quinte essential role in patients especially those on follow-up. This method of consultation avoids direct physical contact, provides continuous care to the community, and reduces morbidity and mortality in the COVID-19 outbreak[17]. Video consultations are relatively easy to set up and are also cost efficient. Health providers and patients should work together to make the best use of current advancement in technology and recognize the importance of telemedicine.

**Practices for safely conducting endoscopy procedures:** Procedures such as bronchoscopy and GI endoscopy are aerosol-generating procedures (AGP). The procedures should be divided into emergent, semi-urgent, and elective[18]. The elective procedures should be deferred until the pandemic subsides in the area. Emergent and semi-urgent may be performed. A negative COVID-19 report within the past 3 days should be mandatory in areas with a high prevalence of COVID-19 infection; since symptoms are often absent in those infected. Bronchoscopy done to collect bronchoalveolar lavage for COVID-19 RT PCR should be used only when other non-invasive sampling techniques are inconclusive, as it would create risk for the health care professionals[19,20].

The shortest procedure should be attempted. Adequate sedation is required and cough should be minimized by drugs taken before the procedure. Nebulization of lignocaine for anesthesia before the procedure should be avoided, as it is also an AGP[21]. A minimum number of people should be present in the endoscopy suite. The most experienced operator should perform the procedure to have the procedure completed in the shortest time. Training of residents should be deferred until the pandemic subsides in the area. Bronchoscopy boxes are now available through which the instrument can be inserted, however, its utility in controlling the infection has not yet been proved. If the box is not available, the endoscope should be inserted via a slotted well-fitted face mask. The endoscopy room should have negative ventilation[22]. The health care professional present in the room should be wearing PPE comprising of N-95 respirator, face shield, hazmat suit, and gloves. Single-use bronchoscopes may be used depending on local availability and logistics. Scopes should be appropriately sterilized and the brushes used to clean should be single-use.

**Precautions against airborne or droplet transmission of COVID-19 – maintaining a safe distance:** According to the WHO guidelines for protecting the HCWs, contact and droplet precautions should be taken by HCWs caring for suspected COVID-19 patients[23]. A medical mask is recommended for routine care, while a respirator (airborne precautions) is recommended if HCWs are conducting an aerosol-generating procedure such as endotracheal intubation, bronchoscopy or airway suctioning, along with droplet precautions[23]. It is also recommended that spatial separation of 1 m (≈ 3 ft) should be maintained with an infected patient, in the belief that large droplets can only spread horizontally to a maximum of 1 m (≈ 3 ft)[24]. However, recent work in this area has raised new questions. A review of published literature revealed the limited scientific data to inform spatial separation guidelines and a growing body of evidence that droplet precautions are not appropriate for SARS-CoV-2[25]. The recent data on SARS-CoV-2 in a hospital ward shows a distance traveled by the virus of at least 4 m (≈ 13 ft), double the assumed safe distance[26]. Thus, further work needs to be done carefully documenting and studying the mechanisms shaping transmission distances.

**General considerations in patient management in COVID era**

1) Should the elective procedure be done?

All elective Surgeries should be deferred & only emergency and semi-emergency (e.g malignancy) can be scheduled. In case of a difference of opinion the final decision should be taken by the Head of the concerned department.

a) The Risk to the HCWs

The main mode of spread of the virus is through droplets, fomites & aerosols. Patients who can be managed with simple procedures such as needle aspirations should not be subjected to surgical procedures (e.g Needle aspiration of Pleural effusion Vs Chest tube

insertion). AGP's (aerosols generating procedures) should be avoided wherever possible. The common AGP's are: Tracheostomy/Endoscopic procedures/ Laparoscopic procedures/ Bronchoscopy/ Sinus surgeries/ Surgeries involving High speed Drills & Electrocautery/Ultrasonic aspirator/ Rectal surgeries/Intubation & Extubation/ Thoracotomies & Chest tube insertions. If a procedure is essential, wherever possible regional anaesthesia should be preferred over GA. Filter devices & negative pressures in the operating room should be used whenever AGP's are performed. The virus persists for a few hours in the air and upto a few days on the surfaces. Hence the rationale of using smoke evacuation machines, filter device & negative pressure in OT room, etc. A minimum of one-hour time gap to be given between two procedures, 30 mins of deep cleaning & 30 mins of Sterilisation/ Fumigation).

Case urgency should be ranked as follows[27]:

Acute: Requiring surgery within 24 hours

Sub-acute: Requiring surgery within 7-10 days

Chronic: Requiring surgery within or more than a month

b) The Risk to the patient

1) There is evidence that surgery in COVID-19 infected asymptomatic patients is associated with a more severe disease manifestation in the post-operative period with a mortality rate of up to 20%. Hence all attempts must be made to treat the problem conservatively wherever possible (e.g. Appendicitis, chloecystitis, ureteric calculus, spinal injury with either no gross neurological deterioration or in cases of total paraplegia where the chances of recovery are very bleak).

2) How should the preoperative assessment be done?

Preoperative assessment should include detailed history including travel history, contact with infected COVID -19 case, or history of fever, myalgia, cough, bodyache, URI. All patients should undergo two COVID RT-PCR based tests in the pre-operative period: first at the time of admission and 2nd one day before surgery with a chest x-ray or CT chest as appropriate before undergoing non-emergency surgeries. All acute emergency cases (where COVID report cannot be obtained before procedure) should be assumed as positive and appropriate precautions should be taken.

3) How much can a negative RT-PCR for COVID be relied upon?

In Stage 3 of the pandemic, the possibility of false-negative should be kept in mind & all due precautions should be taken considering every patient as potentially infected. If there is a clinical suspicion of COVID with a negative RT-PCR report, the patient should be treated as a suspected case rather than a COVID negative case. The Blood counts (DLC) showing relative lymphopenia & monocytosis, suggestive changes in CxR/ CT Chest should be given due importance.

4) What are the pre-operative considerations?

Surgery for COVID negative patients only should be performed in routine OT complex. Surgery for unproven COVID negative should be performed in a designated OT for suspect patients, in a separate OT from the OT complex for negative patients. Surgery for COVID positive patient must be done in a dedicated COVID positive hospital, as far as possible. The OT should have a negative pressure environment, if the same is not available; a high frequency of air exchange (25/hour) is also effective to rapidly reduce the viral load[28]. All OT personnel should take extended standard precautions and wear protective gear such as PPE kits, N-95 masks, with or without a face shield. Each OT complex should have 3-5 OT tables, dedicated nursing staff & other OT Personnel. The operating rooms should not have an interconnected ducting system for ventilation. As far as possible, emergency surgeries should be avoided during the night. All patients belonging to Category A & RT-PCR negative Category B, who have undergone surgery should have their RT-PCR done after 72 hours of operation, to pick up the false-negative patients. Consent regarding accidentally acquiring COVID-19 infection during the hospital stay should be taken & explained. (For Cohort A & possibly for B)

5) What precautionary measures should be taken during surgical procedures?

Positive pressure ventilation should be avoided before intubation. Laminar flow or AC should not be started until intubation is done. Minimal OT personnel should be allowed inside the operating room. The surgical team should wait outside until intubation is done. An adequate amount of consumables such as sutures, drugs, Oxygen cylinders should be kept inside the OT room and

nobody should be allowed to leave or enter the OT room during the procedure. An outside staff member (runner) may be used to provide emergency material during the surgery if any.

Electro cautery should be avoided or should be used at the lowest power settings to avoid smoke, similarly craniotomies & high-speed drills to be avoided. The usage of intra operative drains should be minimal. No Exchange of Room Staff should be allowed.

6) What precautionary measures should be considered in post-operative period?

Only the anaesthesia team should remain in the OT during extubation, remaining members should go out but not remove their PPE's so that they are available in case there is a need. The proper exit sequence from OT should be 1st: Surgical team, 2nd: Patient, 3rd: Anaesthesia team, and 4th: Cleaning & Sanitization crew.

Proper Doffing should be done in the designated area and after doffing nobody is allowed to enter the OT room. The surgical instrument should be sent for autoclave preferably in a separate autoclave facility[28].

**Organizational support to the health care workers:** It is natural that the hospital personals including caregivers, nursing staff, administration, etc., would be stressed by the challenges of a prolonged response to COVID-19, therefore, each healthcare facility should emphasize the physical and mental well- being of the HCWs[29]. The leadership should emphasize on self-care as the most important entity during the COVID response. Conversations with the HCWs could help reduce anxiety, could contribute to a sense of control, and help to build trust. Personnel should be rotated effectively to limit the number of working hours and to ensure adequate rest. Provision of food, decompression time, and personal breaks may be important and may play an important role in maintaining team performance.

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## REVIEW ARTICLE

# A Review for the COVID-19 Vaccines

**Monica Jain**, Anil Bhandari**, Alka Bansal***, Shivankan Kakkar******

## INTRODUCTION

A novel coronavirus, named as severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) was first reported in December 2019 in Wuhan China and caused the highly contagious disease COVID-19. In few months the COVID-19 became a worldwide pandemic. There have been worldwide 8,97,07,115 confirmed cases of COVID-19, including 19,40,352 deaths, reported to WHO, as of Jan 12th, 2021[1].

Presentation of COVID-19 disease is unpredictable for a few asymptomatic and for others it can cause symptoms starting from flu-like to acute respiratory distress syndrome (ARDS), pneumonia and death. After any infection in our body, immune system develops fighting tools to urge over the infection; and system remembers those tools in form of memory cells (T-cells and B – cells) to protect against that disease. When the familiar antigens are detected, B-lymphocytes produce antibodies to attack them. It is still not clear how long these memory cells will protect an individual against COVID-19 due to rapidly mutating CORONA Virus[3].

Till the last month prevention and cure of the COVID by means of social distancing and good quality self-hygiene measures and experimental repurposed drugs were the only measure available.

Today there is a worldwide race flagged off for a safe, and an efficacious vaccine against SARS-COV2. Four vaccines got Emergency Use Authorization (EAU) from FDA (USA) and CDSCO (INDIA), and approximately two hundred vaccines are in various stages of development and in clinical trials.

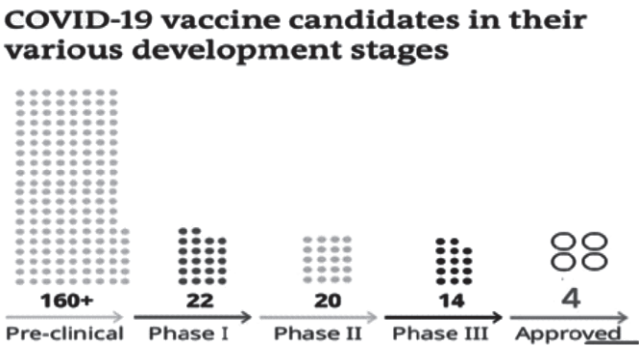


**Figure 1: Vaccine candidates in their various development stages**

This review will primarily focus on the four approved vaccines-Moderna's mRNA -1273, Pfizer'BioNtech; Fosun Pharma's BNT162b2, Astra Zeneca/Oxford's AZD1222 and Covaxin.

### Accelerated COVID-19 Vaccine Development

A new vaccine development typically takes around 10 to 15 years[3], shown by Figure2[2]. The mumps vaccine was the quickest; in five years developed and approved for human use. The exigency of COVID-19 vaccine required a new approach; most of the vaccine candidate opted "Adaptive" and "Compressing" clinical trials models with open digital data share for peer review and quicken approval (*Operation Wrap speed*) to shorten the duration of the complete trial process for the development of the vaccine.

**Figure 2: Duration of vaccine trials Standard v/s accelerated**

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**Vaccine Efficacy or Vaccine Effectiveness[4]:**

Vaccine Efficacy and Effectiveness is interpreted as the proportionate reduction in disease among vaccinated group. Vaccine efficacy is used when a study carried out under idea or standard conditions like clinical trial. Vaccine effectiveness is used when a study is carried out in society.

Vaccine Efficacy Effectiveness (VE) is measured by calculating the risk of disease among vaccinated and unvaccinated persons and determining the percentage reduction in risk of disease among vaccinated persons relative to unvaccinated persons.

The basic formula is written as:

Risk among unvaccinated group-Risk among vaccinated group

Risk among unvaccinated group

OR (Odds Ratio): 1-Risk Ratio

Vaccine Efficacy of 90% indicated a 90% reduction in disease occurrence among the vaccinated group.

Final objective of an efficacious Covid-19 Vaccine[5]


**Diagram adapted from Published Online October 27, 2020 https://doi.org/10.1016/ S1473-3099(20) 30773-8**

**Traditional vaccine Platforms**

The mainstream of vaccines presently licensed for human use are often divided into either virus -based or protein-based vaccines[6]. The virus-based vaccine haveinactivated virus that is not pathogenic or is a live-attenuated virus. Since whole-inactivated viruses never replicate so adjuvants are required to stimulate the immune system. Live-attenuated virus vaccines are designed to decline its pathogenic properties and cause no infection or low to mild infection upon injection. Protein-based vaccine comprises a protein purified from the virus or virus-infected cells, recombinant protein or virus-like particles. Virus-like particle contains the structural viral proteins necessary to form a virus particle, but lack the viral genome and non-structural viral proteins. Protein-based vaccines require the addition of an adjuvant to induce a robust immunologic response. There are a number of restrictions like large quantities of virus required, ought to be grown under Biosafety level 3 and extensive safety testing are correlated with the classic platform that make them less amenable to fast vaccine production during a pandemic[6].

**Gene-based vaccine (GBV) / Novel**

GBV are viral vector vaccine and nucleic acid base vaccines, is a novel vaccine platform. Viral vector vaccines contains a recombinant virus, often attenuated to weaken its pathogenicity, and carrying recombinant genes encoding viral antigen(s) which are cloned using recombinant deoxyribonucleic acid techniques[6].

Nucleic acid-based vaccines can contain DNA or mRNA and may be adapted quickly when new viruses or mutations emerge which is why these were among the very first COVID-19 vaccines to enter clinical trials. DNA vaccines contain a novel artificial DNA construct encoding the vaccine antigen; for maximum efficiency of the artificial DNA construct into cells, injection needs to be followed by electroporation. After uptake into cells, the vaccine antigen is expressed from the artificial DNA construct.

Nucleic acid-based vaccines stimulates a humoral and cellular immune reaction and required two dose one for prime and other to strengthen the immune system.

mRNA-based vaccines work on an equivalent principle as DNA vaccines; However, initial steps of nuclear translocation of the DNA construct and transcription into mRNA is bypassed[6]. Self-replication RNA vaccines are likely to induce protective immunity employing a lower dose, because more vaccine antigen is expressed per cell[7]. In view of poorly stable mRNA these constructs include modified nucleosides to stop degradation. A carrier molecule lipid nanoparticle is important to enable entry of the mRNA into cells.

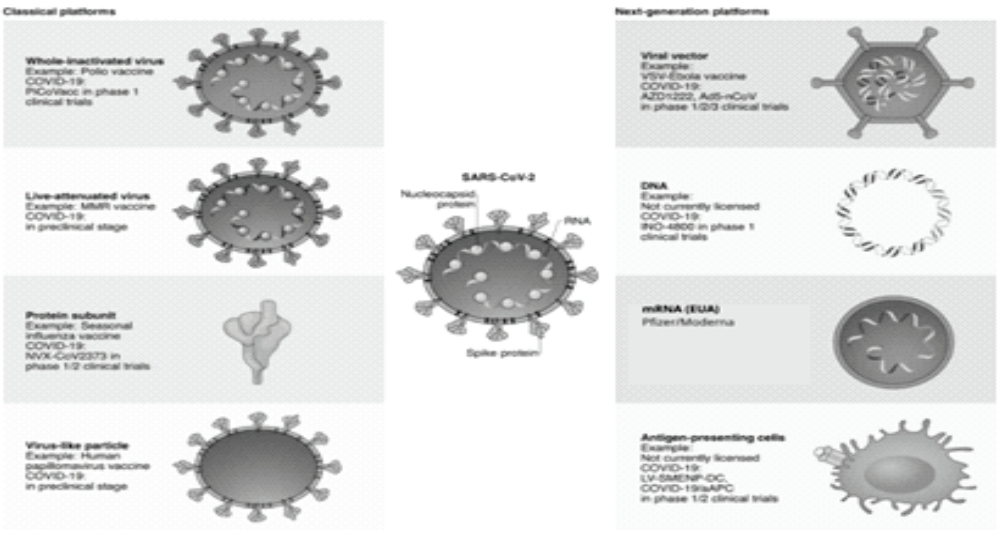


**Figure 3: A schematic representation of the different vaccine platforms (Adapted with permission, from "Next-Generation vaccine platforms for COVID-19" Nature Materials-VOL19-Aug2020-810-820-Debby van Riel and Emmie de Wit).**

## Authorised or Approved Vaccines:

### BNT162b2 (BioNTech and Pfizer) "mRNA"

This mRNA vaccine is delivered in a lipid nanoparticle to express a full-length spike protein. It is administered intramuscularly in two doses three weeks apart[8]. During a large placebo-controlled phase 3 trial[9], this vaccine had 95 percent efficacy in preventing symptomatic COVID-19 at or after day seven following the second dose[9,10].

Local and systemic adverse effects were dose dependent and comparatively common after the second dose; most were of mild or moderate severity. Among participants younger than 55 years, fever occurred in sixteen percent and severe fatigue, headache, and chills occurred in four, three and two percent, respectively[10]. Rates of adverse effects among older participants were slightly lower[9].

After the vaccine was administered to individuals within the UK and US outside a clinical trial, few instances of anaphylactoid reactions were reported[11]. Four rare cases of Bell's palsy were also noted during this trial in vaccine group[10].

### Moderna "mRNA 1273"

This mRNA vaccine was developed and administered to humans within two months of publication of the SARS-CoV-2 genomic sequence. The vaccine utilizes mRNA delivered in a lipid nanoparticle to express a full-length spike protein. It is administered intramuscularly in two doses 28 days apart. mRNA 1273 having 94.1 percent vaccine efficacy in preventing symptomatic COVID-19 at or after 14 days following the second dose. Among adult above 65 years of age, vaccine efficacy was 86.4 percent.

Local and systemic adverse effects were dose dependent and relatively common after the second dose; most were of mild or moderate severity[12]. Among participants younger than 65 years, fever occurred in 17 percent, and severe fatigue, headache, myalgias and arthralgias occurred in 10, 5, 10 and 6 percent, respectively. Adverse effects were less frequent among older individuals; individuals with evidence of prior SARS-CoV2 infection also had lower rates of adverse effects than those without prior infection. Bell's palsy was reported[12] in three cases in vaccine and one in placebo group.

### COVISHIELD "Adenovirus vector"

### CHAdOx1 nCoV-19/AZD1222[13].

(University of Oxford, AstraZeneca, and the Serum Institute of India)

This vaccine is based on a replication-incompetent chimpanzee adenovirus vector that expresses the spike protein. It is given intramuscular and is being evaluated as a single dose or two doses 28 days apart. The levels of antibody titers achieved were higher following two doses; and subsequent studies are evaluating the two-dose regimen. In a study that included older vaccine recipients

(>70 years)[14], the vaccine resulted in similar antibody responses after the second dose as in younger adults.

This vaccine had 70.4 percent efficacy[13] in preventing symptomatic COVID-19 at or after 14 days following the second dose. However, a subgroup of participants inadvertently received a lower vaccine dose for the first of the two vaccine dose, and the vaccine efficacy in this subgroup differed from the rest. Vaccine efficacy was 90.0 percent. Reasons for this difference are uncertain, although the overlapping confidence intervals indicate that the difference is not statistically significant.

In initial-phase trials, fatigue, headache, and fever were relatively common after vaccine receipt and were severe in up to 8 percent of recipients. In the phase III trial[13], there were two cases of transverse myelitis in ChAdOx1 nCoV-19 vaccine recipients. One was thought to be possibly related to vaccination and was described as an idiopathic, short-segment spinal cord demyelination; the other was in a participant with previously unrecognized multiple sclerosis and thought to be unrelated to the vaccine.

COVAXIN "Whole Virion inactivated"

Bharat Biotech-Indian Council of Medical Research (ICMR)-National Institute of Virology (NIV): Approved by CDSCO on 3rd Jan 2021[15].

This indigenous vaccine (BBV152) is a whole-virion propiolactone -inactivated SARS-CoV-2 vaccine. The vaccine strain NIV-2020-770 contains the D614G mutation, which is characterised by an aspartic acid to glycine shift at amino acid position 614 of the spike protein. The vaccine was injected intramuscular in a two dose regimen four weeks apart, and hasto be stored at $2^{O}$-$8^{O}$ C. The most common adverse event was pain at the injection site, followed by headache, fatigue, weakness, rashes, body ache and fever. No severe or life threatening solicited adverse events were reported. The Phase III efficacy trial was initiated in India in 25,800 volunteers, approximate 22,500 participants have been vaccinated across the country and the vaccine has been found to be safe as per the data available till Jan 3rd 2021.

**Table1: Comparison of vaccines.**

| Vaccine Developer | Pfizer | Moderna | AstraZeneca | Covaxin |
|---|---|---|---|---|
| Type | mRNA | mRNA | Adenovirus Vector | Whole Virion inactivated |
| Approval | 11th Dec2020 | 19th Dec 2020 | UK 30st Dec2020<br>India 1st Jan2021 | India 3rd Jan2021 |
| Efficiency | 95% | 94.1% | 70% | Yet to know |
| Dose/ interval | Two dose, 3 weeks apart | Two dose, 4 weeks apart | Two dose, 4 weeks apart | Two dose, 4 weeks apart |
| Storage | -70 C (-94*F) and will last for only 24 hours at refrigerated temperature between 2°and 8° C (36° to 46º F). | -4 F or -20ºC, keep in home Deep Fridge 30 days and at room temperature for 12 Hrs | Normal refrigerated temperature of 2 to 8 °C (36 to46 F) for at least six months | Normal refrigerated temperature of 2-8°C. |
| Side Effects | Fatigue, Headache, Fever, chills, and muscle pain, especially after second dose. | Fatigue, muscle pain, Headache and fever, Worse after second dose | Fatigue, muscle pain, Headache, and fever | Injection site pain, headache, fatigue, weakness, rashes body ache and fever |
| Any Significant Side effect | The CDC has identified 6 cases of anaphylaxis and 4 cases of Bell's palsy in people who received the vaccine and none in placebo group. | Four cases of Bell's palsy were reported in the clinical trials including 3 in the vaccine group and 1 in the placebo group. | One case of transverse myelitis | No significant side effect reported so far. |

**Important Vaccine Candidates in development phase:** NVX-CoV2372[17,18] "Recombinant protein nanoparticle"

Novavaxinvestigational vaccine, NVX-CoV2373, is formed from a stabilized coronavirus spike protein using the company's recombinant protein nanoparticle technology[16]. The purified protein antigens in the vaccine cannot replicate and can't cause COVID-19. The Vaccine also contains a proprietary adjuvant, MatrixMTM. Adjuvants are additives that enhance desired immune responses to vaccine.

NVX-CoV2373 is given in liquid form and may be stored, handled and distributed at above-freezing temperature (35° to 46ºF or 2º-8ºC). The primary safety and immunogenicity analysis indicate that in healthy participants 18-59 years of age, two dose regimens of 5 mcg and 25 mcg of rSARS-CoV-2 plus the Matrix-M1 adjuvant had acceptable safety findings and induced high immune responses[17].

**ZyCoV-D "Plasmid DNA vaccine"**

**Zydus Cadila Healthcare [19]**

**Approved for Clinical trial phase 3 on 3rd Jan 2021[15]**

ZyCoV-D, is an indigenous plasmid DNA vaccine for COVID-19 that focus on the entry membrane protein of the virus. The plasmid DNA when introduced into the host cells through intradermal route, would be translated into viral protein and can elicit a robust immunologic response, mediated by the cellular and humoral arms of the human system.

The DNA vaccine platform is additionally known to show improved vaccine stability, and low cold chain requirement. Further, the platform makes the vaccine easy to manufacture, with minimal bio-safety requirements (BSL-1) and found to be safe in phase 2 trial[15]. The vaccine platform can allow the vaccine to be modified just in case the virus mutates. This makes the plasmid DNA vaccine ideal for access within the remotest regions of the country.

**Sputnik V "Adenovirus Vector Vaccine"**

The Gamaleya National Centre of Epidemiology and Microbiology, Russia

Sputnik V is human adenoviral vector-based platform; it is a two-vector vaccine against SARSCOV2. The vaccine is given intramuscular as an initial adenovirus 26 vector dose followed by an adenovirus 5 vector boosting dose 28 days later. The Sputnik V vaccine efficacy is confirmed at 91.4%[20] supported by data analysis of the ultimate control point of clinical trials. The vaccine showed mild to moderate local and systemic adverse reactions.

In India Dr Reddy's laboratories and Sputnik LLC are jointly conducting Multi-centre, phase II/III adaptive trial.

**Wrapping up for Kaizen:** Although vaccines clinical trials data are publicly available, however, caution on the effectiveness of immunization programs remains. How long does immunity last? Will the vaccines prevent viral transmission? Are those vaccines safe and efficacious in vulnerable population like children, immune compromised patients and pregnant women who haven't been included in the trials?

Vaccines are going to be a masterstroke for the control of COVID-19. We have to successfully implement the mass immunization program for entire adult population without compromising the vaccine effectiveness; nonetheless, worldwide supplies are going to be a conundrum.

The mass inoculation programme and its effect won't be instantaneous, as COVID-19 cases and deaths are still on rise across the planet. The non-pharmaceutical interventions to constrain the spread of SARS-CoV-2 that the worldwide population has by now become adapted to will have got to remain in situ for a little longer time.

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## DRUG UPDATE

# Sodium Oligomannate: a Promising Hope in Treatment of Alzheimer's Disease Through Suppression of Gut Dysbiosis

**Dhirendra Kumar Mahawar*, Monica Jain**, Shivankan Kakkar*, Arun Singh***, Anil Bhandari*****

## INTRODUCTION

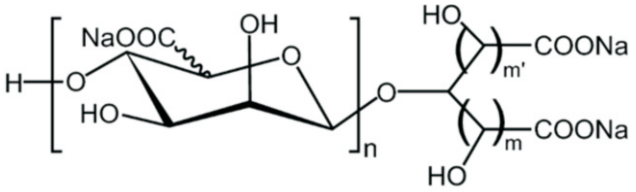
**Sodium oligomannate,** Is seaweed-based cocktail of linear oligosaccharides (ranging from dimers to decamers) derived from marine (brown) algae and an orally administered drug for Alzheimer's disease (AD).

Marine algae can source some distinctive metabolites which have varied health benefits. Their pharmacological characteristics, namelyanti-inflammatory, anti-oxidant, protein clearance and anti-amyloidogenic potentials, protect against neuroinflammation, oxidative stress, and deregulated proteostasis in neurodegenerative disorders. Alzheimer's disease involves two proteins: amyloid-βand tau, wheneither reaches abnormal levels in the brain, it leads to the formation of plaque, which gets deposited between neurons, damaging nerve cells[1].

Recently, many studies show the interaction between gut microbiota and host immune system[2,3]. The dysbiosis in gut flora may disturb host immune system and induce inflammation[4]. There is a growing evidence that gut microbiota is correlated with the incidence of Alzheimer's disease, Parkinson's disease, depression, and other central nervous system disorders. During the preclinical studies, the drug has shown to improve cognitive function by restructuring the balance of gut microbiota, inhibiting the anomalous increase of specific metabolites of this microbiota, reducing central and peripheral inflammation, amyloid-β deposition and hyper phosphorylation of Tau protein in AD[5].

In November 2019, after 22 years of research, this drug finally got conditional approval from China's National Medical Products Administration (NMPA) for treatment of mild to moderate Alzheimer's disease[6]. It is developed and manufactured by Shanghai Green Valley Pharmaceuticals, Ocean University and Shanghai Institute of Materia Medica. A**lternative names of** Sodium oligomannateare*GV-971, Hamput Sodium, Mannut Sodium, Oligomannate, Sodium oligomannurarate, Nine Phase One,* Sodium oligo-β-1 → 4-D-mannuronic acid-*O*-dicarboxylic acid.

## CHEMICALSTRUCTURAL




Chemical structure of sodium oligomannate. n = 1~9; m = 0, 1, 2; m′ = 0, 1

Chemical Name: Sodium oligo-β-1 → 4-D-mannuronic acid-*O*-dicarboxylic acid

ATC code (WHO)- N06D (Anti-Dementia Drugs)

## MECHANISM OFACTION

Sodium oligomannate can penetrate the blood brain barrier (BBB) through glucose transporter 1 (GLUT1) and inhibit amyloid-βfibril formation and destabilizing the fibrils into nontoxic monomers. Although the absolute mechanism of action remains unclear, sodium oligomannate controls neuroinflammation and decreases memory impairment by suppressing gut dysbiosis and the associated phenylalanine/isoleucine accumulation (Figure.1). Significant changes seen in regulation in amino acid related metabolic pathway and enzymes especially phenylalanine related pathway in GV-971 treated Tg Mice and inhibition of neuroinflammationalso seen. Microglial activation, brain cytokine level, Aβ plaque

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deposition and tau protein phosphorylation reduced in GV-971 treated Tg mice. Th1 cells in brain of recipient C57BL/6 WT mice decreased after Feces transplantation from GV-971 treated Tg mice[1].

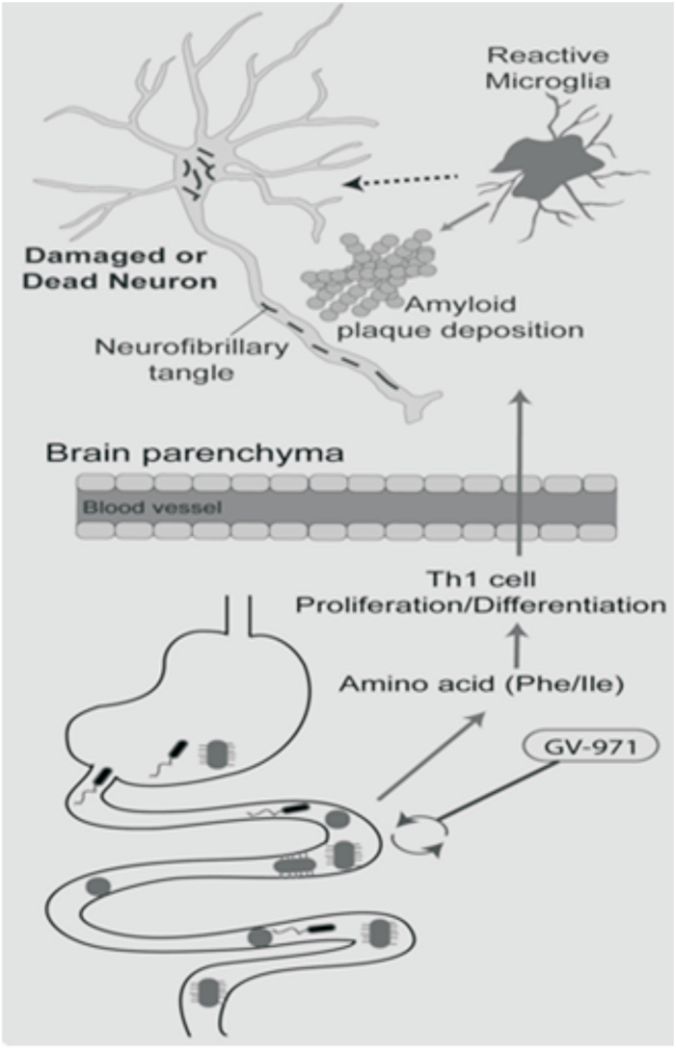


**Figure 1: Mechanism of action: sodium oligomannate**

In a phase II pilot study, in patients with Alzheimer's disease, there was an elevation of amyloid-β levels in the cerebrospinal fluid (CSF) following sodium oligomannate treatment, suggesting an important role in amyloid-β clearance into CSF[7]. There was a differential reduction in the cerebral glucose metabolic rate by sodium oligomannate. While in the phase II trial, the cerebral glucose metabolic rate in left orbito-frontal gyrus and precuneus &right posterior cingulate gyrus, and hippocampus were low, in the phase III trial, the lower rate was found in superior and inferior parietal gyrus, angular gyrus, and the anterior wedge in the brain[8].

## PHARMACOKINETICS

Sodium oligomannate has low oral absorption and peak plasma concentration achieved at 5.4 hours. The apparent volume of distribution is 9608.7 L after 600 or 750 mg single oral dose. Plasma half-life ranges from 11-22 hours. The study data about metabolism and excretion of sodium oligomannate is not available. After twice daily dosing for five days, the apparent clearance was found 117.4-158 Liter/hr[9].

## SIDE EFFECTS AND TOLERABILITY

Sodium oligomannate was well tolerated in clinical trial phase- II and III with minimal side effects[7,10]. The most common adverse drug reaction (ADR) in sodium oligomannate group was dry mouth, hematuria and elevated ALT and AST, bilirubin and low density lipoprotein level. Severe ADR (pneumonia) was found in one patient (0.2%). One patient with dizziness, one with seizures and one with gastritis have suspended the treatment while another seven patients left the treatment due to ADR[9].

## DOSE

Sodium oligomannate is available in oral dosage form as capsule in the strength of 150 mg. The dose of this drug in Alzheimer's disease is 450 mg twice daily.

Cost: A prescription of 42 capsules of sodium oligomannate costs 895 Yuan (Approx. INR 10000)

## RESULTS OF CLINICAL TRIAL

In CT-phase II (NCT01453569), (n=255) received sodium oligomannate or placebo for 24 weeks in the dose of 600 mg/900 mg per day. The parameter of disease was accessed by Alzheimer's Disease Assessment Scale (ADAS-cog12) and Clinician's Interview- Based Impression of Change-Plus (CIBIC+). ADAS-cog12 score was not significantly different from baseline to 24 weeks treatment in the treatment group of 600mg and 900 mg vs placebo groups. CIBIC+ score was significantly improved at 24 weeks treatment with 900 mg/day vs placebo[7].In CT phase III (NCT02293915), (n=818) received sodium oligomannate 450mg twice a day or placebo for 36 weeks. At the 4 weeks onward, the ADAS-cog12 score was significantly improved in treatment group as compared to placebo group. But CIBIC+ score was not significantly improved[9,10].

## CURRENT STATUS

02nd November 2019: The China National Medical Product Administration (NMPA) provisionally permits the use of sodium oligomannate to treat individuals with mild to moderate Alzheimer's disease.

03rd April 2020: The FDA approves IND (Investigational New Drug) application for sodium oligomannate in Alzheimer's disease.

27th April 2020: Shanghai Green Valley Pharmaceuticals plans to submit a New Drug Application (NDA) to the FDA for Alzheimer's disease by 2025.

27th Oct 2020: Shanghai Green Valley Pharmaceutical starts the phase-III GREEN MEMORY trial for Alzheimer's Disease in United States.

Till now, there is no cure for Alzheimer's disease, the medications only help control the symptoms and/ delay the progression of the disease. With the recent approval of Sodium oligomannate, a fresh ray of hope has emerged among the people affected with this disease.

However, sodium oligomannate lacks the global data of effectiveness and therefore requires large scale global trials before it can receive approval from the (FDA).

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## CASE REPORT

# Lactating Adenoma - Cytological Dilemma

**Asha Goyal*, Chandrika Gupta**, Shruti Bhargava*****


## ABSTRACT

Lactating adenoma is pathological benign tumor of breast that is frequently associated with pregnancy and lactation. Lactating adenoma needs to be differentiated from other breast masses like galactocele and it can also mimics as carcinoma. History, cytological and histopathological examination helps in diagnosis of the disease. Cyst macrophages, secretory epithelial changes (isolated epithelial cells) and eosinophilic fluid in background is feature of lactating adenoma. Only cyst macrophages and eosinophilic fluid in the background suggest galactocele on cytopathology which is also common in pregnancy and lactation. Here we presented a case of lactating adenoma in 21 year old lactating women, which was diagnosed as galactocele on cytology and later on histopathology turned out as lactating adenoma.


## INTRODUCTION

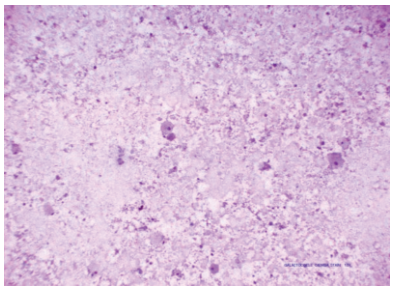
Pregnancy is associated with many physiological and pathological changes in the breast. Lactating adenoma is one of such pathological benign tumor of breast that is frequently associated with pregnancy and lactation[1,2]. They can occur in any trimester but are common in third trimester of pregnancy and lactation. They are common in young primiparous women in the second or third decade[1]. Lactating adenoma needs to be differentiated from other breast masses like galactocele and it can also mimics as carcinoma. History, cytological and histopathological examination helps in diagnosis of the disease.

Here we presented a case of lactating adenoma in 21 year old lactating women.

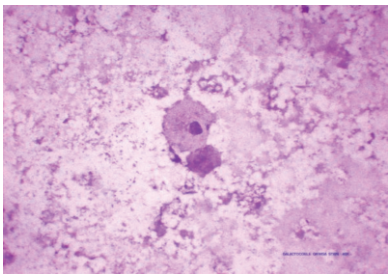
## CASE REPORT

A 21 year old lactating female presented with chief complaints of non tender mobile lump measuring 2 x 2 cm palpable in upper outer quadrant of left breast since 2 months. The size of lump was gradually increasing. Patient had taken antibiotic treatment but had no relief.

A provisional diagnosis of galactocele was made by clinical examination and sent for FNAC procedure. On FNAC thin milky white fluid was aspirated. The smears were stained with H and E stain as well as Giemsa stain. On microscopic examination smears shows numerous cyst macrophages in the background of eosinophilic fluid with fat droplets. The diagnosis was given suggestive of galactocele based on these findings. Subsequent excision was done and lump was diagnosed as lactating adenoma on histopathology. Microscopy showed capsulated tumor tissue arranged in tubular and trabecular pattern. Individual cells were hyperplastic epithelial cells showing hyperchromatic nuclei and moderate eosinophilic cytoplasm and intracytoplasmic vacuoles.



A(10x Giemsa stain )



B (40x Giemsa stain)

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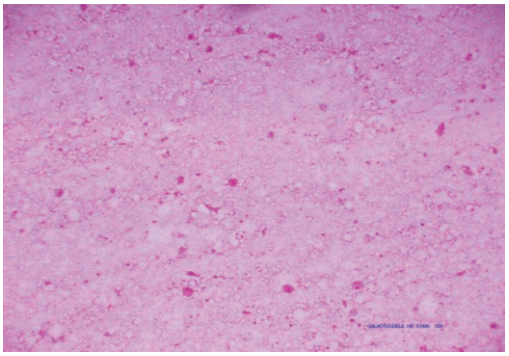
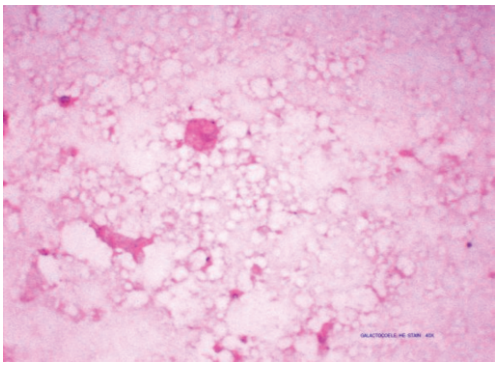


C(10xH&Esatin)



D( 40x H&E stain)

**Figure 1: A,B, C, D - Fine needle aspiration cytology shows cyst acrophages in background of eosinophilic fluid suggestive of Galactcele**

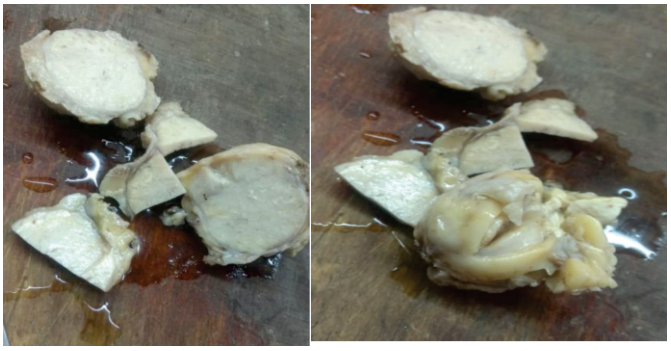
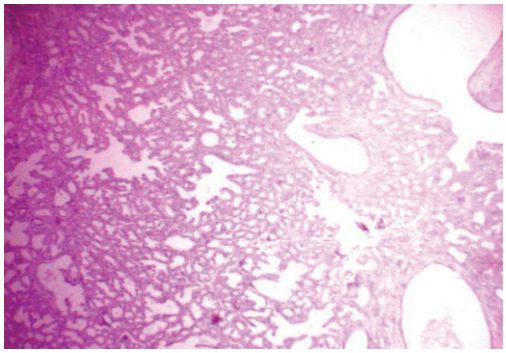
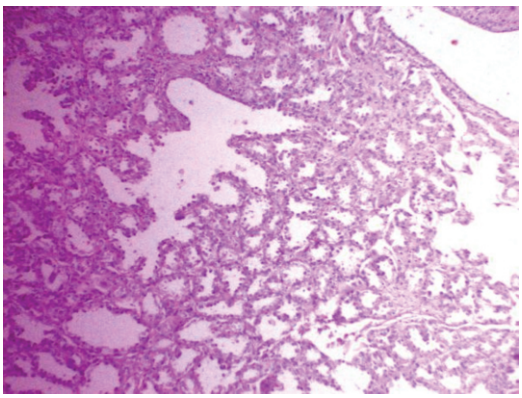


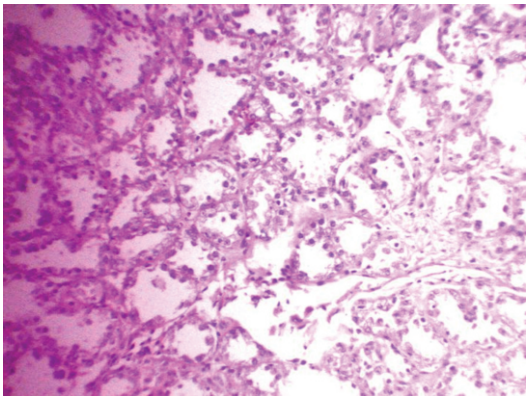
**Figure 2: (A,B) Gross picture of lump, cut surface is capsulated and yellow.**



**A**



**B**



**C**

**Figure 3: (A, B, C) Lactating adenoma 4x, 10x , 40x. (H&E stain)**

## DISCUSSION

Lactating adenoma is a benign tumor of breast typically occur during lactation or third trimester of pregnancy. It is characterized by typical change of secretory epithelium leading to formation of a well differentiated benign tumor. It is also known as tumor of pregnancy because changes seen in the form of secretion in these regions resemble lactational change of pregnancy[3]. Our case present clinically as galactocele and female was lactating since one year. On FNAC, type of aspirate and cytological features, both lead towards the diagnosis of galactocele. Clinical history and clinical diagnosis also favour our cytological diagnosis. On excision of lump histopathology was done and the case was confirmed as lactating adenoma. Our case was misdiagnosed as galactocele on cytopathology because clinical presentation and aspirate was in favor of galactocele and smears showed cyst macrophages and eosinophilic fluid in background which leads towards the diagnosis of galatocele. Secretory epithelial changes (isolated epithelial cells) were not seen in cytosmear may be due to

needle, not touching the area (limitation of FNAC). Subsequent excision was done and on histopathology diagnosis was lactating adenoma.

Lactating adenoma present duing pregnancy and lactation as galactocele. Cytology with accurate clinical history will help in accurate diagnosis. Definitive diagnosis made by histological examination. Cut surface is lobulated and tan yellow[4,5]. Histopathology shows network of large alveolar spaces separated by fine fibrovascular trabeculae. The trabeculae are lined with typical cuboidal cells containing prominent cytoplasmic vacuoles.

There are two proposed theories about the pathogenesis of lactating adenomas. One suggests that a lactating adenoma is a de novo lesion unique to pregnancy or alternatively lactating adenomas may result from adenomatous or lactational transformation of preexisting lesions, such as fibroadenomas, tubular adenomas, or hamartomas, which undergo lactational changes under hormonal influences[6].

## CONCLUSION

Lactational adenoma should be kept in mind when a young pregnant or lactating female present with confusing painless breast lamp that increases rapidly. The histopathology is essential to establish the diagnosis as cytopathology may lead to misdiagnosis as in our case due to same clinical history, same type of aspirate and overlapping features of cytology in galactocele and lactating adenoma.

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## CASE REPORT

# Adrenal Myelolipoma in Non Functional Adenoma

**Santosh Sharma*, Deepika Hemrajani**, Kusum Mathur*****


## ABSTRACT

Adrenal myelolipoma is rare benign neoplasm which is generally considered hormonally inactive neoplasm and composed of mature adipose tissue and normal haematopoietic cells. Adrenal cortical adenoma and myelolipoma rarely found together in the same gland. Dignosis is incidental due to its asymptomatic nature[1]. We reported a case of 71 year male with complain of lower urinary tract symptoms, who on imaging study showed an adrenal mass of size 38 x 32mm likely to be adenoma. It was detected incidentally because of its nonfunctional nature. Later on the size of mass increased and due to hemorrhage in the tumor and radiological study a diagnosis of adrenocarcinoma was given for which surgery was done and right adrenalectomy specimen sent for histopathological examination. After gross and microscopic examination reported as adrenocortical adenoma with myelolipoma which is rare to occur simultaneously. This case requires correct diagnosis and management of the adrenal mass.


**Key words:** Adrenocortical adenoma, Myelolipoma, Incidentaloma

## INTRODUCTION

In the literature, myelolipoma was described first by the German scientist E Uber Gierke in 1904 but C Oberling was first to use the term myelolipoma in 1929.[5] Adrenal myelolipoma is a benign neoplasm composed of varying proportion of mature adipose tissue and hematopoietic elements

However sometimes adrenal myelolipomas and adrenal cortical adenoma are found together and if the cortical adenoma is non-functional then they are detected incidently[1]. Adrenal myelolipoma and non functional adrenal cortical adenoma are rare in the same gland[1]. Myelolipomas are composed of mature adipose tissue and normal haematopoietic cells. In fact, myelolipoma can now be easily detected because of improved techniques such as ultrasound, CT and MRI and widespread use of imaging[1].

## CASE PRESENTATION

We report a case of 71 yr old male, presented to the S.M.S hospital OPD with complains of urinary frequency, urgency and low stream of urine. On CECT scan KUB there was right adrenal soft tissue density mass approx 38 X 32 mm? Adenoma detected incidentally. On investigating hormone study was normal. Cortisol-4.67(normal range 4.5-22.4ug/dl DHEA-82(normal range-male 80-560ug/dl, aldosterone and 24 hr. urinary metanephrine was 95.71ug (normal <350) Patient was kept under observation. After 6 month there was increase in size of right adrenal mass and haemorrhage on CT imaging study. MRI study revealed features of adrenal cortical carcinoma. Hormonal studies were within normal limits. Right adrenalectomy was performed and sent for histopathological examination.

Grossly it was a single well encapsulated, yellow, firm already cut open globular soft tissue piece measuring 4.5×3×3 cm, with capsule, yellow, lobulated soft in consistency, along with extensive areas of haemorrhage.

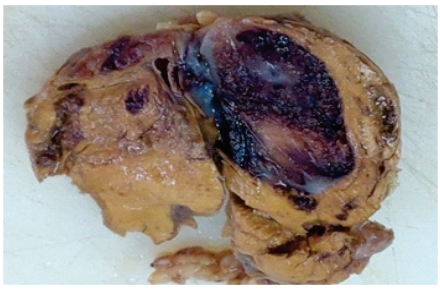

**Figure 1: Gross pictures, Showing pale,gray lobulated tumor with haemorrhage and surrounded by a capsule**

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Microscopically, the tumor showed capsulated, lobulated tumor composed of cells with clear cytoplasm and uniform round nucleus with no nuclear pleomorphism. No necrosis, mitosis, capsular or vascular invasion seen. Areas of osseous metaplasia, haemorrhage and hematopoietic cells seen showing presence of myelolipoma in addition.

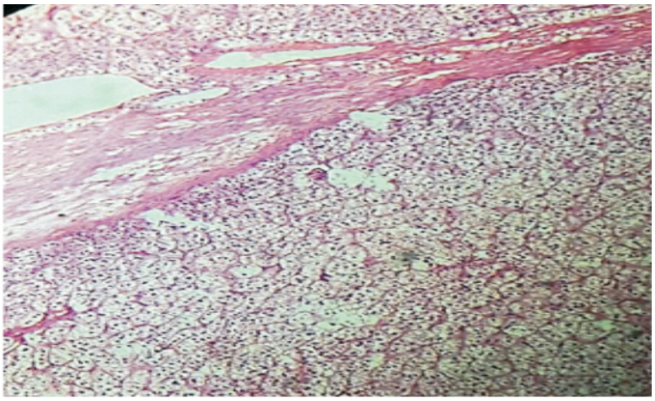

**Figure 2: H/E stained Showing capsule and uniform cords of cells with pale and clear cytoplasm(100X).**

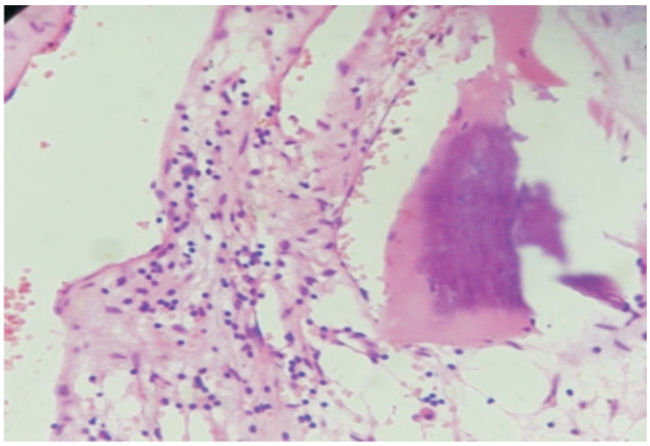

**Figure 3: H/E stained showing bony trabeculae and fibrofatty tissue with haematopoitic elements(100X).**

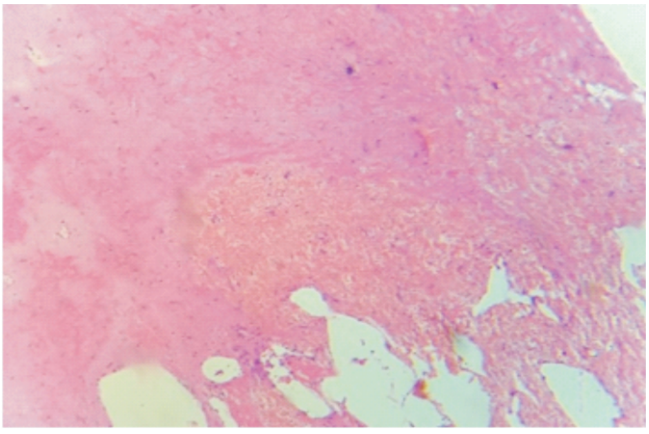

**Figure 4: H/E stained showing haemorrhage(100X)**

## DISCUSSION

Myelolipomas are small, asymptomatic and non-functional tumors. Although the benign nature of these lesions is proved, it is unclear how these tumors develop. There are different explanations about this according to a widely accepted theory; pathogenesis of myelolipomas occurs in response to stimuli, such as, necrosis, infection or stress, reticuloendothelial cells of blood capillaries in the adrenal glands with metaplasia[2]. Myelolipomas affects both sexes equally, between the age of 50 to 70 yr[3]. Case was 71 yr old. According to reported cases, examined patients were all women. Most of the cases originated from the left side. But in our case, the tumour was located in right adrenal region. Three radiological patterns for adrenal myelolipomas are described: isolated adrenal myelolipomas, myelolipomas with haemorrhage and complex lesions with small myelolipomatous foci within other adrenal tumours (non-functional adenoma, adrenocortical adenoma, Conn's syndrome) often with extensive calcifications[4].

The dfferntial diagnosis includes; Renal angiolipoma which is more common, contains vascular and leiomyomatous elements in addition to fat. Extramedullary hematopoiesis is not encapsulated or well circumscribed and fat cells are not an integral component of the process, moreover it is symptomatic usually with splenomegaly and hepatomegaly, associated with severe anemia, myelofibrosis and myeloproliferative disorders. Retroperitoneal lipomas are rare, multiple, slow growing and abnormal proliferation of adipocytes. In Liposarcoma, fat cells are seen within the soft tissue. Diagnosis is by histologic examinatation of the tissue. Lipoblasts are often present in these cells with an abundant clear multivacuolated cytoplasm and an eccentric darkely staining nucleus that is indented by the vacuoles. For the diagnosis of these adipocytic tumors of the adrenal gland, CT and sonography are sensitive and important imaging techniques. Major difference between myelolipomas and other adrenal neoplasm is the presence of mature fat. Adrenocortical adenoma versus carcinoma - Adrenal tumors are usually not biopsied prior to surgery, so diagnosis is confirmed on examination of the surgical specimen by a pathologist. Grossly, adrenocortical carcinomas are usually large and with a tan-yellow cut surface, areas of hemorrhage and necrosis. On microscopically, the tumor usually displays sheets of

atypical cells with some likely resemble with the cells of normal adrenal cortex. The presence of invasion and mitotic activity help to differentiate small cancers from adrenocortical adenomas.

In our case there was myelolipoma which was found under a capsule, in focal area along with hemorrhage. The size of the tumors may vary from a few millimeters to 34cm and they account for about 8% of adrenal incidentalomas[5]. Myelolipoma may be associated with various adrenal pathologic conditions like adenoma, carcinoma, pheochromocytoma, idiopathic hyperaldosteronism, Addison's and Conn's disease. So diagnosis of myelolipoma is impotant as there is risk of spontaneous rupture with retroperitonal haemorrhage[6,7]. In our case there was misdiagnosis in MRI finding due to extensive haemorrhage so histopathology was required for diagnosis the of myelolipoma.

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## CASE REPORT

# Congenital CMV Infection with CMV Pneumonitis

**Nishant Gopaal*, Jagdish N Sharma**, Vijay Agarwal***, Priyanshu Mathur***, Laxman Jadoun******

**ABSTRACT**

The human cytomegalovirus (CMV) is widely distributed among the human population as one of the most common causes of congenital infections. Congenital CMV infection is seen in approximately 1% of all newborns of which 10% are symptomatic at birth and is a leading cause of sensorineural hearing loss, vision impairment, varying degrees of intellectual disability and delayed psychomotor development.

Here, we present the case of a 7-month-old male child with symptomatic congenital CMV infection presenting with interstitial pneumonitis, bilateral sensorineural hearing loss, chorioretinitis, periventricular leukomalacia, persistent lymphocytosis and failure to thrive. Congenital CMV infection was confirmed by Urine PCR and supported by serology, MRI Brain, BERA, fundus examination and clinical history. Marked improvement in signs and symptoms was observed after treatment with Valganciclovir was initiated according to protocol.

**Keywords:** Congenital CMV infection, TORCH infections, pneumonitis, microcephaly, sensorineural hearing loss, chorioretinitis, periventricular leukomalacia, failure to thrive

**INTRODUCTION**

Congenital CMV infection is seen in approximately 1% of all newborns of which 10% are symptomatic at birth[1]. Of the symptomatic newborns almost 70-80% develop late complications that may include sensorineural hearing loss, vision impairment, dental abnormalities, varying degrees of intellectual disability and delayed psychomotor development[2,3]. Congenital CMV infection has emerged as the leading non genetic cause of sensorineural hearing loss[4]. Congenital CMV infection may present with several nonspecific manifestations, although pneumonitis is considered a rare manifestation.

**CASE REPORT**

A 7-month-old male child was admitted with complaints of fever and respiratory distress for one month. The mother had a history of mild grade fever during the 1st trimester for which no treatment was sought. All antenatal ultrasounds were normal. The child was born full term, normal vaginally delivered, to a primigravida mother and was small for gestational age with birth weight of 2.15 kg. The child was admitted at live day two for neonatal jaundice. Patient had a history of recurrent hospital admissions with complaints of fever and failure to gain weight.

The patient had microcephaly (head circumference<-3SD), weight<-3SD, mild hepato-splenomegaly and bilateral fine crepitations were noted in all lung fields. CNS and cardiovascular systems were found to be normal. Gross motor and verbal milestones were delayed

X-ray revealed ground glass opacities and patchy areas of consolidation involving all lobes of bilateral lungs (Figure 1). USG abdomen showed mild hepato-splenomegaly. Patient had high total leucocyte count (29,000/$mm^3$) with lymphocytic predominance (60%) and toxic granules in peripheral blood film. SGOT/SGPT was mildly elevated (114U/L, 98U/L), serum bilirubin was normal.

HRCT chest showed multiple nodular areas of patchy consolidation, ground glass haziness and smooth interstitial septal thickening diffusely scattered in bilateral lung fields suggestive of interstitial viral pneumonitis (Figure 2,3). The patient tested negative for COVID-19 and an alternative cause for pneumonitis was sought.

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A history of failure to thrive, developmental delay, microcephaly, hepatosplenomegaly, persistently elevated TLC and recurrent viral pneumonitis prompted a search for congenital TORCH infections, and a TORCH profile for mother and child was ordered. The child tested positive for CMV with high serum IgG (101 U/ml) and IgM (54 U/ml) titres. Urine RT-PCR for CMV which was done for confirmation also came positive. The mother tested positive for CMV IgG antibodies. Clinical presentation along with investigations proved the diagnosis of Congenital CMV infection.

A search for other known manifestations of congenital CMV was done. A 3-T MRI Brain showed mild diffuse cerebral atrophy in bilateral frontal lobes with bilateral periventricular leukomalacia and ex-vacuo dilatation of lateral ventricles (Figure 5). BERA revealed bilateral moderate-severe sensorineural hearing loss with fluctuation in the latency of wave V. Direct ophthalmoscopy showed a prominent macular scar with multiple chorioretinal scars in the periphery suggestive of chorioretinitis. 2-D Echo was found to be normal.

Oxygen inhalation by high-flow nasal cannula was given for 15 days due to tachypnea and low oxygen saturation. Treatment was initiated with ganciclovir at 6 mg/kg per dose administered intravenously every 12 hours. This regimen was continued for 4 weeks with serial monitoring of CBC, LFT, RFT for detecting toxicity. There was marked improvement in signs and symptoms. Fever and respiratory distress gradually resolved and the pneumonitis like picture in chest X-ray gradually improved (Figure 4). Patient was the shifted to oral valganciclovir (16 mg/kg/dose bd) after 4 weeks when the patient was clinically stable and able to take oral medications and therapy was planned for the next 6 months.

## DISCUSSION

Congenital cytomegalovirus (CMV) infection occurs worldwide, with a prevalence of 0.6 percent in developed countries[5]. The risk of vertical transmission, symptomatic disease and long-term sequelae to the foetus is far higher with primary maternal infection (32%) than with recurrent infection (1.4%)[5,6].

Infants with congenital CMV infection are categorized into symptomatic and asymptomatic based on the clinical findings. Infants with virologically-confirmed congenital CMV and at least one end-organ symptom are classified as symptomatic. Approximately 10% of neonates with congenital CMV infection have symptoms at birth. The common clinical presentations at birth include petechiae (50%-75%), jaundice at birth (40%-70%), hepatosplenomegaly (40%-60%), SGA (40%), microcephaly (35%), sensorineural hearing loss (35%) (SNHL)[7,9]. Congenital CMV infection presenting as pneumonitis is considered a rare manifestation[7,8]. Transaminase and bilirubin levels typically peak within the first 2 weeks of life and can remain elevated for several weeks while thrombocytopenia subsides by one month of age[7]. Less commonly haemolytic anaemia, lymphocytosis and neutropenia has also been observed. Around 10 percent of newborns with symptomatic congenital CMV infection end up with a fulminant course due to viral-associated hemophagocytic syndrome or severe end-organ disease of the CNS, liver, lungs or bone marrow[10].

CMV pneumonitis is estimated to occur in less than 1% of infants with congenital CMV infection with a more fulminant course in case of immunocompromised infants[8]. Congenital CMV pneumonitis may persist for several months if left untreated and can result in development of bronchopulmonary dysplasia due to associated factors such as secondary bacterial pneumonitis, requirement of oxygen inhalation or mechanical ventilator support[8].

Late presentations in infants include hearing loss, vision impairment, intellectual disability and delayed psychomotor development. Ophthalmologic examination reveals chorioretinitis and/or optic atrophy in approximately 10% of symptomatic infants[7]. Neuroimaging findings commonly include periventricular calcifications, lenticulostriate vasculopathy, white matter disease, ventriculomegaly, migrational abnormalities, or periventricular leukomalacia[11]. SNHL is detected in 30-40% of infants with symptomatic disease and 10% of asymptomatic cases[2]. The hearing loss associated with symptomatic congenital CMV is often progressive and profound[6].

A high degree of suspicion must be observed for neonates presenting with petechiae, SGA, thrombocytopenia, hepatosplenomegaly, unexplained jaundice or direct hyperbilirubinemia at birth, sensorineural hearing loss, chorioretinitis or typical features on MRI Brain, and such patients must be subjected to TORCH profile and must be tested for CMV.

Antenatal testing can be carried out by viral culture or CMV DNA detection in amniotic fluid by PCR. Post-natal detection can be performed by running PCR on

either urine, saliva or blood of the neonate. Measurement of CMV genome load may be useful for diagnosis as well as treatment response to ganciclovir therapy. Urine sample is preferred since specificity is low for saliva samples and not all patients are viremic[12]. Serologic testing for CMV IgM/IgG antibody is not preferred as the sole diagnostic test, because of low sensitivity and specificity. Establishing a diagnosis of congenital CMV infection beyond the first year of life is generally not feasible because of low viral loads.

Intravenous (IV) ganciclovir and its oral prodrug, valganciclovir, are the first-line antiviral agents of choice for treatment of congenital CMV disease[13]. Antiviral therapy should be initiated for symptomatic patients as soon as the diagnosis is confirmed, preferably within one month of postnatal life[14]. Treatment must also be offered for asymptomatic patients with isolated hearing loss. Therapy with Valganciclovir must be continued for duration of 6 months according to current guidelines[14].

Monthly CBC, LFT, RFT must be done for monitoring of therapy related toxicity. Monitoring of Urine CMV PCR must also be carried out to look for response to therapy.

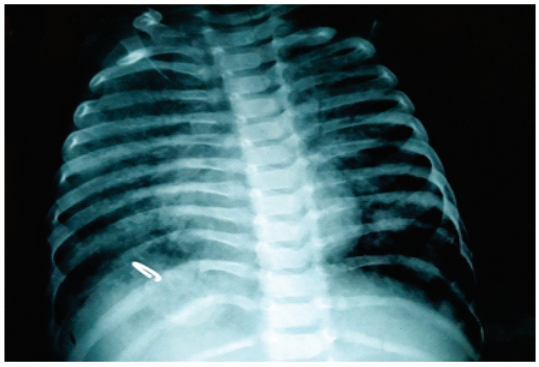

**Figure 1: X-Ray Chest with B/L pneumonitis**

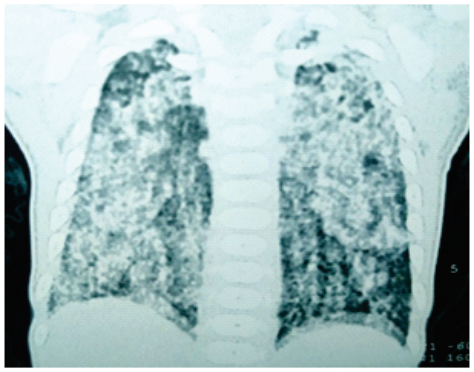

**Figure 2: CECT Chest with B/L ground glass appearance s/o Interstitial Pneumonitis**

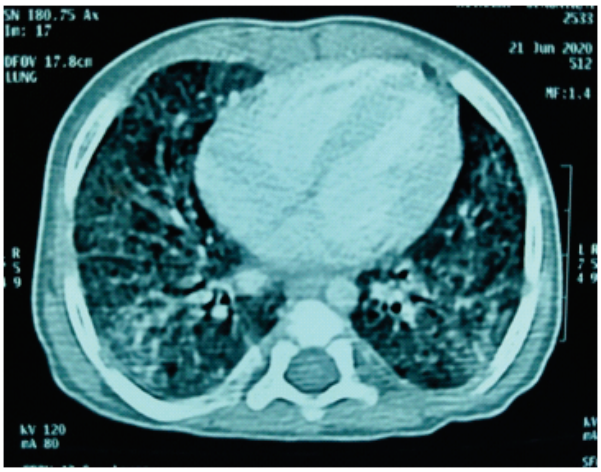

**Figure 3: HRCT Chest s/o Interstitial Pneumonitis**

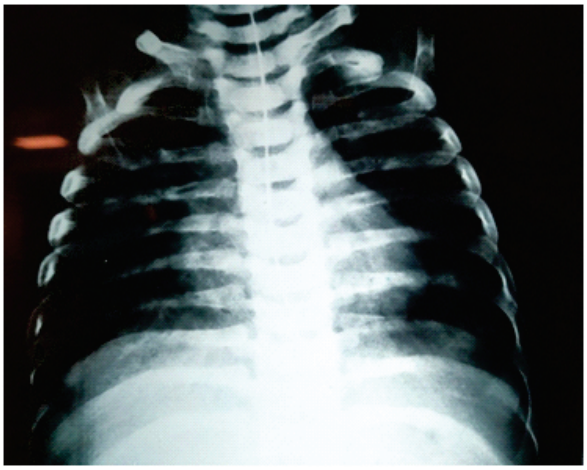

**Figure 4: X-Ray Chest -Post therapy with Valganciclovir**

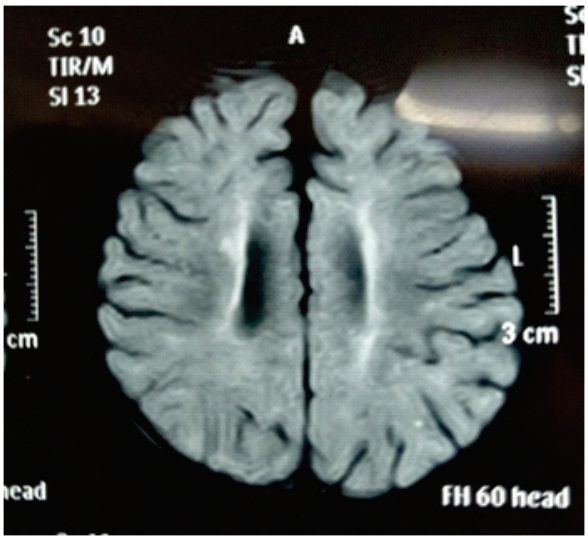


**Figure 5: MRI Brain- Periventricular leukomalacia**

## CONCLUSIONS

Newborns and infants presenting with petechiae, SGA, thrombocytopenia, hepatosplenomegaly, unexplained jaundice or direct hyperbilirubinemia at birth, sensorineural hearing loss, chorioretinitis, unexplained pneumonitis or typical features on MRI Brain should be evaluated for TORCH infections. Congenital CMV infection can rarely present with pneumonitis manifesting as respiratory distress, and early diagnosis and intervention is important to prevent complications like failure to thrive, BPD, chorioretinitis, SNHL and intellectual disability.

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## CASE REPORT

# Minimal Invasive Management of A Giant Neonatal Ovarian Cyst: A Case Report

**Praveen Mathur*, Priyanka Mittal**, Dinesh Barolia**, Rahul Gupta***, Gunjan Sharma******

**ABSTRACT**

Incidence of antenatal and neonatal ovarian cysts is on a continuous rise due to the improvement in imaging techniques as well as routine use of antenatal ultrasound scanning. We discuss here the laparoscopy assisted management of a case of a giant neonatal ovarian cyst, presenting with obstruction and respiratory distress. The procedure was well tolerated by the patient. Moreover, this technique can be applied in a resource challenged setting and in the beginning of learning curve, as it is not completely intracorporeal. Laparoscopy is supposed to have both diagnostic and therapeutic value with minimal morbidity and ovarian salvage whenever possible. In the hands of an experienced and skilled surgeon, laparoscopy is a good alternative to laparotomy in neonates requiring surgical intervention for ovarian cysts.

**KEYWORDS**

Laparoscopy, Neonate, Ovarian cyst, Cosmesis.

**INTRODUCTION**

Ovarian cysts are the most frequently encountered abdominal tumors in female fetuses and newborns[1]. With the advancements in radiographic techniques and the extensive use and easy access to ultrasonography, ovarian cysts are easily detected in the antenatal scans[2]. It has been well validated in literature that an abnormal exacerbation of the physiologic process heralds the presence of ovarian cysts in the fetus and newborn[3]. However, at the time of birth, maternal hormonal stimulation is withdrawn, amounting to spontaneous resolution of ovarian cysts within the first year of life[4]. Giant ovarian cysts as described in literature are cysts measuring more than 10 cm in size in their largest diameter[5]. While most of the simple cysts resolve, lesions that are giant, complex, or symptomatic may cause complications and might need surgical intervention. This substantiates the role of postnatal ultrasound to re-evaluate the antenatally diagnosed lesions. Approach towards management, whether mini-laparotomy or laparoscopy, remains controversial. Laparoscopic management represents an evolution in management of this pathology. With this intent, author reports a case of giant simple ovarian cyst in a neonate managed with laparoscopic assistance and try to review the available literature.

**CASE REPORT**

We report a referred case of a 5 days old female neonate, birth order 1, antenatally not supervised, delivered by normal vaginal route, to non-consanguineous parents, after 39 weeks of uneventful gestation. The mother had no history of any drug intake, no history of gestational diabetes and no history of congenital anomalies in the family. According to birth records, the baby cried immediately after birth, and had an Apgar score of 10 at 5 minutes. The patient passed meconium (in small amount) immediately after birth; and passed urine 6 hours after birth. Feeds were initiated, but the patient developed complaint of bilious and non-projectile vomiting, abdominal distension and laboured breathing on day 2 of life.Feeds were withheld. The patient was referred on day 5 of life. Baby's weight on presentation was 3.2kg. The patient was dehydrated and had laboured breathing and tense and distended abdomen. The apex beat was located in 5$^{th}$ intercostal space, mid-axillary line anteriorly. However, there was no evident cyanosis and murmur. According to referral slip, there was very infrequent passage of stools over this span of 5 days.

A plain abdominal X ray showed the bowel loops

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shifted towards right. The electrolytes were deranged. Coagulation profile and liver function tests were within normal limits. Septic screen was negative. Ultrasound examination showed a hypo-echoic cystic lesion originating from left ovary, measuring 15×15 cm, shifting the whole bowel upwards and towards right side. Contrast enhanced computerised tomography (CECT) abdomen showed 15×15 cm cystic lesion originating from left ovary. (Figure 1)Tumor markers ( β human chorionic gonadotrophins, alpha fetoproteins) were negative.

The patient was rehydrated, electrolyte imbalance was corrected. Patient underwent laparoscopic surgery after 72 hours of optimization. Two 5mm ports were inserted (optical port-transumbilical and working port in left lower quadrant). Pneumoperitoneum was created. (Flow 2L/min and pressure 6 mm of Hg). A large well defined cyst originating from left ovary was identified. Right ovary and both the fallopian tubes were normal. Cyst was aspirated via working port and copious amount of serous fluid was aspirated. Adhesions to distal small intestine were divided. Cyst wall was delivered via working port and was excised. (Figure 2) Ovary was preserved.Hemostasis was ensured. Port closure was done in layers. Patient was reversed and extubated. Histopathological report of specimen was suggestive of simple follicular cyst. The patient is doing well and well healed scar with good cosmesis; and no evidence of recurrence on USG evaluation over a close follow up of 6 months.

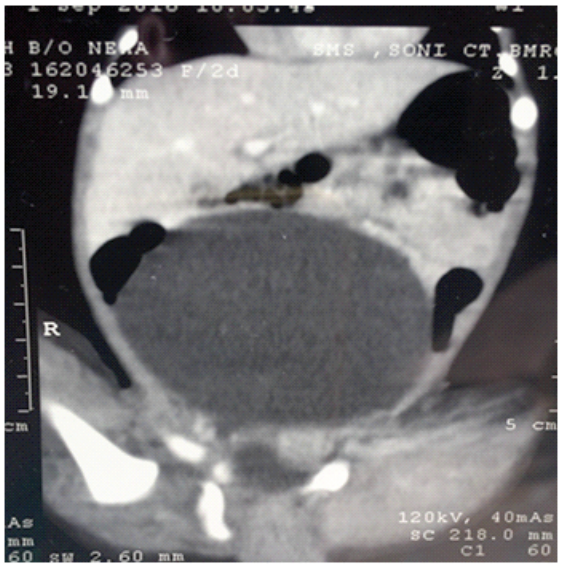


**Figure 1 – CECT abdomen showing huge ovarian cyst occupying the whole abdominal cavity and and displacing the bowel loops.**

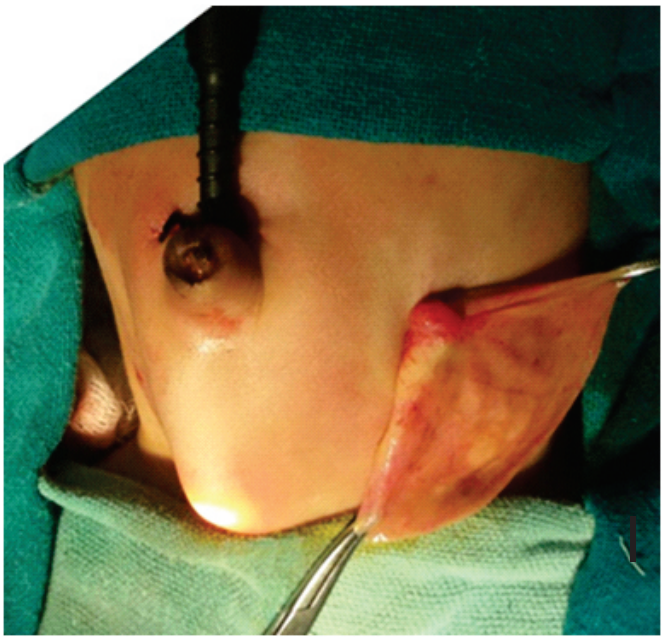

**Figure 2 – Operative photograph showing ovarian cyst wall retrieved via working port post needle aspiration.**

## DISCUSSION

Nussbaum's classification divides neonatal ovarian cysts into simple or uncomplicated (completely anechoic) and complex or complicated (characterized by fluid debris level, clot, septa, and echogenic wall) suggestive of torsion[6]. The presentation of ovarian cysts can range from being completely asymptomatic to the complications like compression of other viscera, torsion with loss of ovary, rupture or haemorrhage. Torsion is the most common (50-78%) complication as neonatal ovary is suspended over a relatively longer pedicle and is commoner in larger cysts[7]. Torsion is known to occur more frequently during fetal life than postnatally. Therefore, to effectively prevent torsion, treatment of fetal ovarian cysts should be performed antenatally, although criteria for prenatal decompression still need to be evaluated[6]. Antenatal aspiration is not routinely practised and deemed to be less successful as continued maternal hormonal stimulation is thought to lead to recurrence[7]. Ultrasound-guided needle aspiration of the cyst can also be a viable alternative to surgery, but this option is associated with more chances of cyst rupture and peritonitis. Also the chances of recurrence are more with needle aspiration[8]. A rare complication of ovarian cysts is autoamputation, which presents as a wandering mass in the abdomen[6]. In newborns, ultrasound has imperative role in evaluation of ovarian torsion; but the role of clinical evaluation cannot be underrated[6]. Symptomatic and complex cysts should

be excised regardless of the size[7]. The management of asymptomatic, uncomplicated cysts still stays controversial[9]. Small simple ovarian cysts under 4 cm in diameter can be observed carefully with serial ultrasonography. However, all complicated ovarian cysts and simple cysts over 5 cm in diameter in addition to smaller cysts less than 5 cm showing no decrease in size should be considered for surgical indication to rescue the ovarian tissue[10]. Laparoscopy is a new evolution in the management of ovarian cysts. However, the major goal of any treatment modality stays optimal ovarian preservation.

Laparoscopy is both diagnostic as well as therapeutic. It is well tolerated by newborns; with better cosmesis at the same time. Additionally, it allows aspiration of the cyst, cystectomy, decapsulation of the ovary, stripping of cysts and, if necessary, oophorectomy. It demands some adjustments in instruments and insufflation pressures (6-8 mm Hg) with constant monitoring of end-tidal CO2. In our case, operating time was 60 minutes. There were no intraoperative or postoperative complications. And the patient was discharged within 24 hours after surgery. Hence, our case demonstrated the feasibility of the minimally invasive technique using two ports for ovarian cystectomy in a neonate.

## CONCLUSION

The laparoscopic approach provides the advantages of early recovery, shorter hospital stay, good cosmesis and less propensity of adhesion formation. In addition to being diagnostic, it can also be used for aspiration, deroofing, cystectomy and oopherectomy in cases of ovarian cysts. Hence, laparoscopy is an important tool in the armamentarium of management of neonatal ovarian cysts.

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## CASE REPORT

# A Rare Case Report of Sirenomelia-the Mermaid Syndrome

**Mukesh Mittal*, Apoorva Singh**, Ashwini B, Dinesh Kumar**


## ABSTRACT

Sirenomelia is a rare congenital fetal anomaly with characteristic feature of complete or partial fusion of lower limbs. It is commonly associated with renal agenesis, absent external genitalia, anorectal malformations, sacrococcygeal agenesis, single umbilical artery and oligohydramnios. Here, we report a rare case of antenatal detection of sirenomelia at 33 weeks of gestation with associated anomalies.


**Key-words**: Mermaid syndrome, Sirenomelia, oligohydramnios, single umbilical artery

**Key Messages**: Sirenomelia is a rare congenital anomaly involving fusion of lower limbs associated with severe oligohydramnios, renal agenesis and single umbilical artery.

## INTRODUCTION

Sirenomelia, also known as mermaid syndrome due to its resemblance to mermaid in Greek mythology. It is a rare congenital structural anomaly with its incidence being 2-3 cases per 1 lacs births with male and female ratio of 3:1. About 300 cases have been reported worldwide of which 8 are from India[1]. Key feature of sirenomelia is single or fused lower limbs which can be associated with other severe anomalies like bilateral renal agenesis, agenesis of external genitalia and anorectal atresia. Most of the cases are incompatible with life.

## CASE HISTORY

A 24 years old primigravida with 33 weeks of gestation presented for the first time to our hospital and was referred to us for USG. Her personal and family history was unremarkable. She was of low socio-economic status. There was no history of any medication/infections in early period of pregnancy. No history of consanguineous marriage.

Antenatal USG (Figure 1) showed breech presentation with severe oligohydramnios. Fetal kidneys and bladder were not visualised. There was a single lower limb with single femur and single short bone below knee likely tibia. (Figure 2) There was a hypoechoic lesion in fetal pelvis with calcification and lower fetal spine was not visualised. Due to severe oligohydramnios characterisation of mass was not possible. Because of presence of calcifications within the mass, the probable diagnosis was meconium pseudocyst. Single umbilical artery was found. Examination of brain and heart was normal.

3D USG was done which showed a single short lower extremity with absence of foot confirmed our diagnosis. (Figure 3)

The lady delivered a newborn of 2.1kg at 36 weeks of gestation via normal vaginal delivery. Neonate was still born. Physical examination of newborn showed single lower extremity with absence of foot, absence of external genitalia, anal opening and single umbilical artery (Figure 4). Autopsy and radiograph of the newborn was denied by the parents. Intrapartum and postpartum period of mother was uneventful.

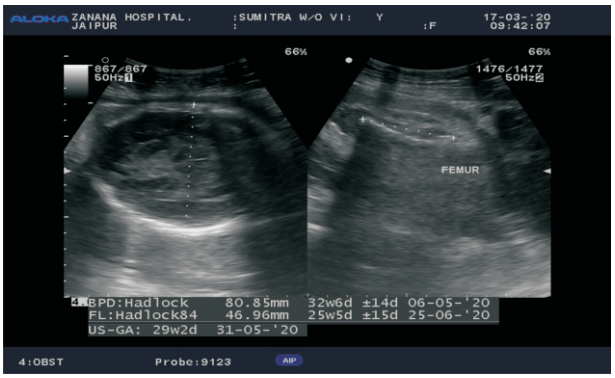


**Figure 1: USG showing fetus of gestational age 33 weeks with small single femur.**

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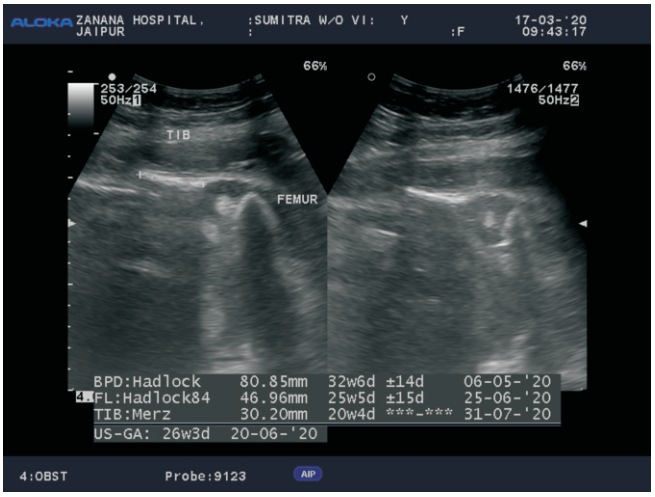


**Figure 2: USG showing single lower limb with single short tibia.**

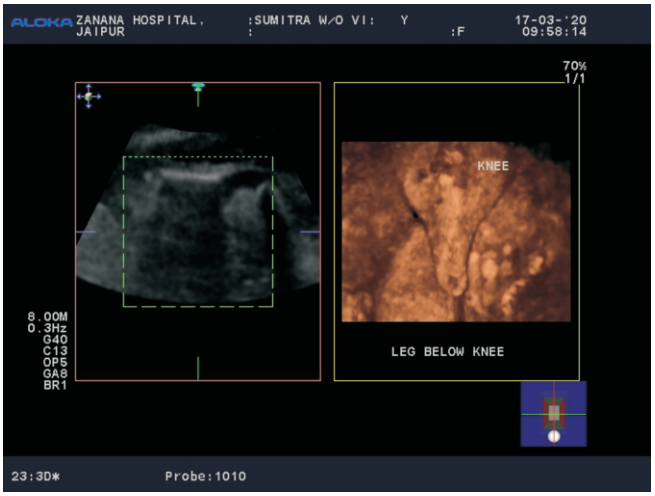


**Figure 3: 3D USG showing blind ending single short lower extremity with absence of foot.**

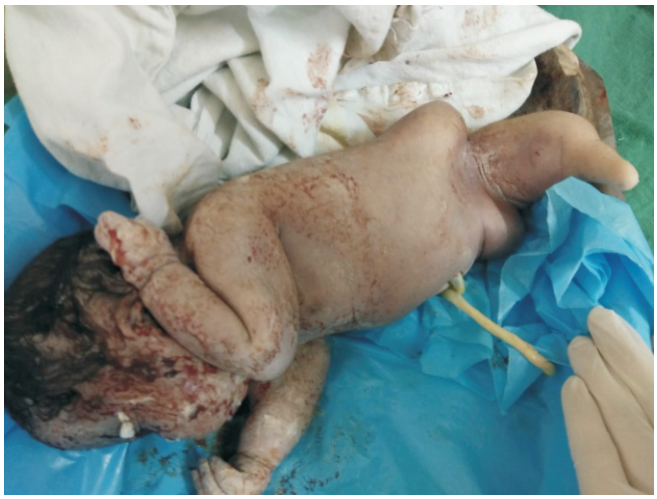

**Figure 4: Fetus showing single lower extremity and absence of foot suggestive of sirenomelia.**

## DISCUSSION

Sirenomelia, also known as sirenomelia sequence, is a severe malformation of the lower body characterized by fusion of the legs and a variable combination of visceral abnormalities. Owing to visceral abnormalities, sirenomelia is usually incompatible with life[2]. Sirenomelia can be a part of caudal regression sequence and VATER association[3].

Most cases occur for non-apparent reasons, as seen in this case. However, maternal diabetes mellitus[4], genetic predisposition, environmental factors (tobacco use, retinoic acid and heavy metal exposure), and vascular steal phenomenon with the single vitelline umbilical artery diverting blood supply and nutrients from the lower body and limbs have been reported as possible etiological factors[5-8].

Sirenomelia can be diagnosed as early as 13 weeks by using high resolution or colour Doppler sonography. Foetal MRI can also help in diagnosis. Oligohydraminos acts as an alerting sign[9]. Sirenomelia has been classified into 7 types by Stocker and Heifetz[10].

| TYPE | CHARACTERSTICS |
|---|---|
| I | All thigh and leg bones are present |
| II | Single fibula |
| III | Absent fibula |
| IV | Partially fused femurs, fused fibula |
| V | Partially fused femurs |
| VI | Single femur, single tibia |
| VII | Single femur, absent tibia |

According to this classification this case belonged to type VI.

3D ultrasound can be a potential tool in diagnosing this condition.

Sirenomelia is a fatal condition and can be detected at an early gestation on ultrasound, pregnancy can be terminated to prevent high risk pregnancy and maternal stress.

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